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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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USE OF ANTIBIOTICS

Transcription of a Panel Meeting

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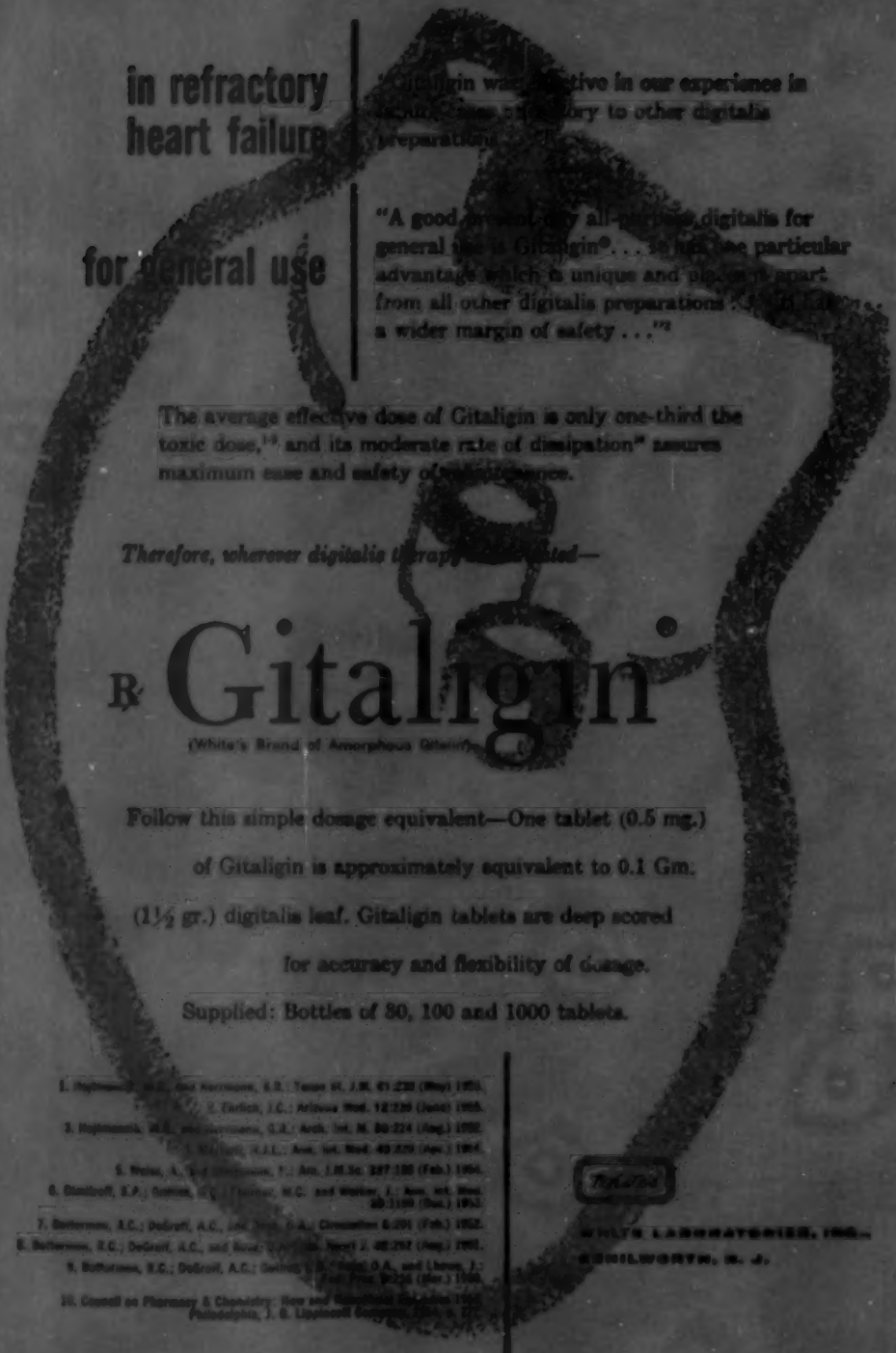

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1. Hejtmancik, M.R., and Herrmann, G.R.: Texas St. J.M. 47:230 (May) 1951.
2. Durlacher, J.C.: Arizona Med. 12:239 (June) 1955.
3. Hejtmancik, M.R., and Herrmann, G.R.: Arch. Int. M. 90:224 (Aug.) 1952.
4. Wallace, W.J.L.: Ann. Int. Med. 40:279 (Apr.) 1954.
5. Weiss, A., and Hutchinson, F.: Am. J.M.Sc. 227:185 (Feb.) 1954.
6. Steinhoff, E.P.; Gorton, H.C. and Walker, J.: Ann. Int. Med. 39:1189 (Dec.) 1953.
7. Batterman, R.C.; DeGroff, A.C., and Ross, O.A.: Circulation 5:251 (Feb.) 1952.
8. Batterman, R.C.; DeGroff, A.C., and Ross, O.A.: Am. Heart J. 46:252 (Aug.) 1953.
9. Batterman, R.C.; DeGroff, A.C.; Gerlach, E.S.; Ross, O.A., and Lewey, J.: Ann. Phys. 9:124 (Jan.) 1956.
10. Council on Pharmacy & Chemistry: New and Nonofficial Remedies 1956. Philadelphia, J. B. Lippincott Company, 1956, p. 57.

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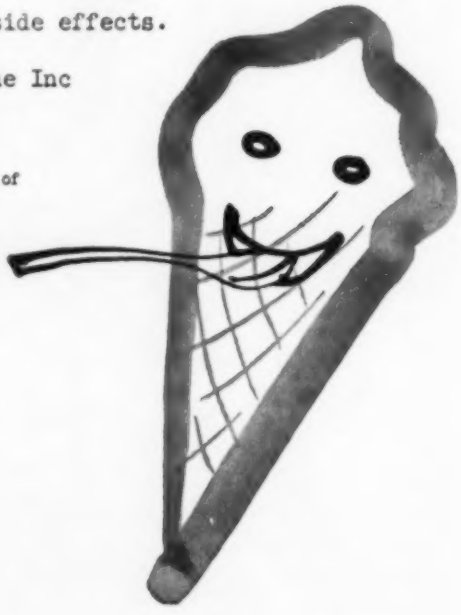

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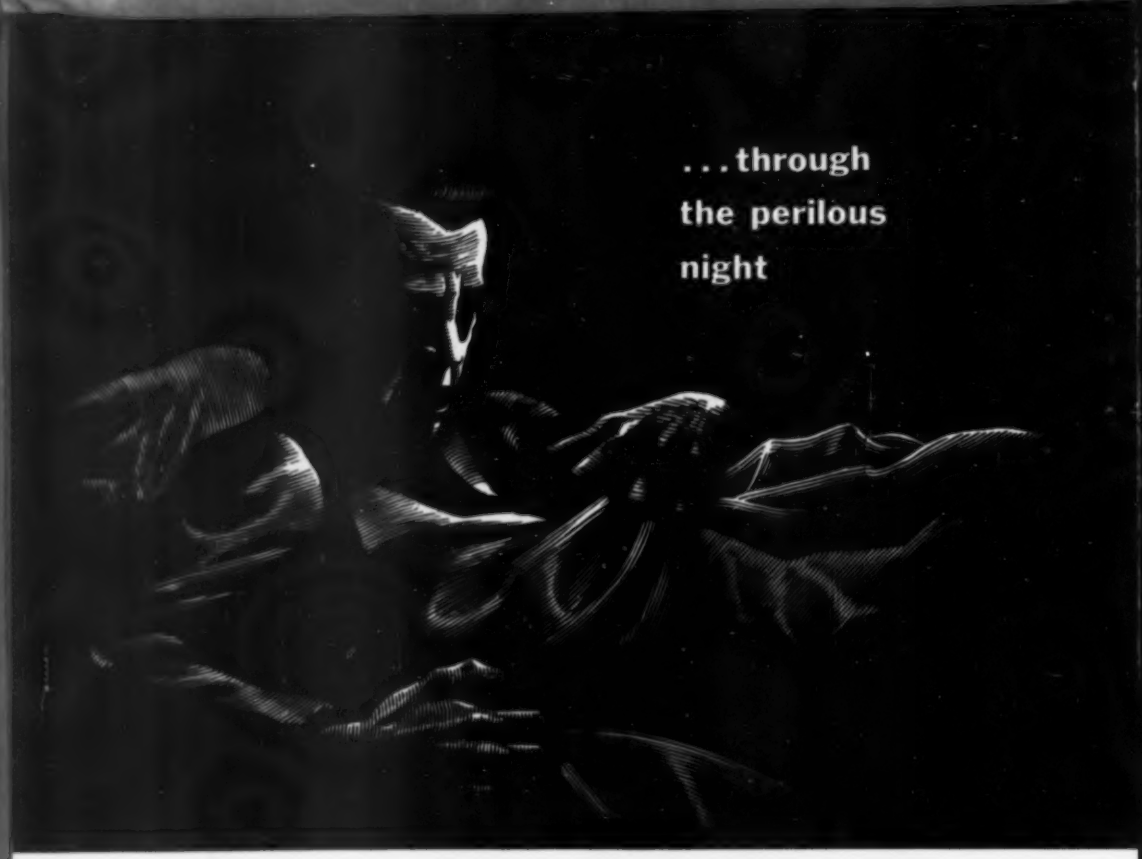

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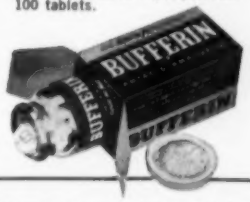

References: 1. Fremont-Smith, P.: J.A.M.A. 158:386, 1955. 2. J.A.M.A. 141:124, 1949. 3. M. Times 81:41, 1953.

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 31, NO. 9 SEPTEMBER 1955

THE ACUTE DIARRHEAL DISEASES OF BACTERIAL ORIGIN*

FRANCIS S. CHEEVER

Professor of Microbiology, Graduate School of Public Health, University of Pittsburgh

ACUTE diarrhea of sudden origin is a distressing complaint of not infrequent occurrence in general practice and it is one which usually prompts the sufferer to consult his physician. As such it represents a serious and important challenge to the diagnostic acumen of the practicing physician, for not only may the syndrome be the result of a variety of direct insults to the gastrointestinal tract, but in addition it may be a secondary manifestation of a disease process located outside the bowel.

Before passing to a brief discussion of the primary causes of acute diarrhea it should be emphasized that the distinction between diarrhea and dysentery is a clinico-pathological rather than an etiological one. Frequent bowel movements accompanied by the passage of blood, pus or mucus are usually referred to as *dysentery* by the physician, while if these latter elements are missing in spite of frequent evacuations of the bowel, *diarrhea* is the clinical term used to describe the condition. If several individuals are infected simultaneously with the same organism some may develop diarrhea and others dysentery according to these

* Presented at the 27th Graduate Fortnight of The New York Academy of Medicine, Oct. 28, 1954.

TABLE I—COMMON CAUSES OF ACUTE DIARRHEAL DISEASE IN MAN

Class	*Examples*
Microbial Agents	Protozoa Bacteria Viruses
Metallic Poisons	Cadmium Sodium fluoride Zinc
Poisonous Foods	Mushrooms Raw sprouted potatoes Rhubarb leaves
Antimicrobial Agents	Chlortetracycline (Aureomycin) Oxytetracycline (Terramycin)

definitions. Essentially the terms describe the degree of reaction of the host to the specific injury.

As may be seen from Table I a variety of agents may be the cause of acute diarrhea. The group of microbial agents is probably the most important one; its principal members are bacteria and protozoa although recent clinical and laboratory studies have furnished strong presumptive evidence that certain viral agents may cause a similar clinical picture.[1] Non-living agents which may cause acute diarrhea include poisonous metallic salts such as sodium fluoride, cadmium and zinc, and foods such as mushrooms or raw sprouted potatoes which in themselves may exert an intensely irritating effect upon the gastrointestinal tract. Another group of agents has assumed considerable importance in recent years. These are the broad-spectrum antibiotics such as chlortetracycline (Aureomycin) and oxytetracycline (Terramycin), and to a lesser extent chloramphenicol (Chloromycetin).[2] Their administration by mouth may be followed by diarrhea of varying severity, probably due to a direct irritating effect on the bowel. This condition must be carefully differentiated from the more serious staphylococcal enteritis which may develop in the course of antibiotic therapy as a result of changes in the bacterial flora produced by the specific antimicrobial agent.

Bacterial agents regarded as important causes of acute diarrhea fall

TABLE II.—BACTERIAL AGENTS CAUSING ACUTE DIARRHEAL DISEASE IN MAN

Organism	*Disease*	*Incubation Period*
Vibrio comma	Cholera	1-3 days
Shigella (numerous types)	Bacillary dysentery	1-3 days
Salmonella (numerous types)	Gastroenteritis	12-24 hours
Staphylococcus aureus (usual type)	Gastroenteritis	1-4 hours
Streptococcus fecalis	Gastroenteritis	2-18 hours
Escherichia coli (Types 055:B5 and 0111:B4)	Gastroenteritis	Variable

into six genera: Vibrio, Shigella, Salmonella, Staphylococcus, Streptococcus and Escherichia (Table II). In the case of the first two the diseases caused by them are well recognized clinical entities. Thus the cholera vibrio (Vibrio comma) is the causative agent of cholera, and similarly the dysentery bacilli (various species of Shigella) are the etiological agents of bacillary dysentery. In contrast, the various species of Salmonella and certain strains of Staphylococcus cause acute gastroenteritis of varying severity which is commonly designated as food poisoning, since contaminated food is the usual means by which these organisms gain entrance into the gastrointestinal tract. The use of this term is unfortunate in at least two respects. In the first place "food poisoning"[3, 4] is a broad loosely-used term applied to diarrheal disease caused by the ingestion of food contaminated with a variety of animate and inanimate agents (protozoa and bacteria on the one hand and zinc and cadmium on the other, for example) and to diarrheal disease caused by foods which are in themselves irritating to the gastrointestinal tract. In the second place one important type of bacterial food poisoning, botulism (caused by Clostridium botulinum) is characterized by signs and symptoms almost entirely referable to the central nervous system as opposed to the gastrointestinal tract. A more accurate term is gastroenteritis qualified by the name of the organism causing it—e.g., salmonella gastroenteritis.[5]

The role of streptococci and of coliform bacilli in the pathogenesis

of diarrheal disease is less well defined. Streptococcus fecalis has been reported to have been the causative agent of a relatively small number of outbreaks of diarrheal disease,[3, 5] but the evidence incriminating it has been circumstantial at best, and more work must be done before its etiological role can be determined. Similarly a growing body of circumstantial evidence strongly suggests that certain serotypes (055:B5 and 0111:B4) of Escherichia coli may on occasion cause outbreaks of infantile diarrhea.[6, 7] In this case also, further clinical, laboratory and epidemiological investigations are required before a firm judgment can be passed on the importance of these organisms as potential agents of diarrheal disease in man.

The present discussion is limited chiefly to a consideration of bacillary dysentery and of gastroenteritis of salmonella and staphylococcal origin, since in the United States today these are the most important forms of diarrhea caused by bacterial agents. Cholera still exists in epidemic form in parts of the Orient such as India and China but except for rare sporadic cases occurring in seaports it has not been present in this country for years. As previously mentioned, the importance of Streptococcus fecalis and Escherichia coli as etiological agents of diarrheal disease remains to be determined.

Bacillary Dysentery

Bacillary dysentery is an infectious disease involving chiefly the colon and less often the distal ileum. The etiological agents are the various species comprising the genus Shigella. These organisms are short non-motile gram-negative rods, whose biochemical activities are characterized by an inability to ferment lactose* and to split urea, and in general little tendency to produce H_2S. In the United States the more important etiological agents are Shigella sonnei and the various serological types of Shigella flexneri. Man represents the only significant host and the disease is most prevalent under conditions of environmental sanitation conducive to the pollution of food and water supplies with fecal material of human origin, or where poor habits of personal hygiene favor the direct transfer of fecal material from one individual to another.

The average incubation period of bacillary dysentery is forty-eight hours. Abdominal cramps are the first manifestations of the disease, followed in a few hours by diarrhea which in all but milder cases is

* An important exception is Shigella sonnei, which is a late lactose fermenter.

characterized by the passage of gross pus and mucus, frequently accompanied by blood. In severer cases fever is always present during the acute stage. As the disease progresses the frequent evacuations lose their copious character and the generalized abdominal cramps are succeeded by tenesmus. Headache and lassitude are frequent complaints but vomiting is relatively rare except in children. The severity of the disease may vary from a slight diarrhea lasting but a few hours to a prostrating dysentery simulating cholera.

Although the presumptive diagnosis of bacillary dysentery may be made on clinical grounds alone, especially if similar cases are occurring in the same community, laboratory assistance is required to confirm the diagnosis. These procedures may be outlined as follows:[8]

1. Microscopic examination of the stool employing coverslip preparations of mucoid material emulsified in saline. The characteristic highly cellular exudate of bacillary dysentery shows a marked predominance of polymorphonuclear elements as opposed to the mononuclear exudate of amebic dysentery. Furthermore, failure to find motile trophozoites of Endamoeba histolytica makes the diagnosis of the latter condition less likely.

2. Isolation and identification of the etiological agent. Although cultures should ideally be taken with the aid of the sigmoidoscope, the rectal swab technique of Hardy, Watt and DeCapito[9] offers the most practicable procedure in most cases. In situations where this is impossible, resort must be had to stool culture. Since the organism is a delicate one, the specimens should be brought to the laboratory as soon as possible for streaking out on plates of selective media. In the case of stool specimens flecks of mucus are selected for streaking, since the dysentery bacilli are usually found in greatest numbers in this material. Identification of suspicious organisms is carried out by means of biochemical and serological tests. It is obvious that the final identification of the dysentery bacillus as to type requires laboratory facilities rarely found outside hospitals or health departments.

The treatment of bacillary dysentery falls into three categories as shown in Table III: general supportive measures, restoration and maintenance of fluid and electrolyte balance, and elimination of the etiological agent by means of antimicrobial therapy.

General Supportive Measures: Bed rest and a liqiud or soft low residue diet are recommended during the acute phase of the disease.

TABLE III.—THERAPY OF ACUTE BACILLARY DYSENTERY

Category	*Specific Measures*
General measures (supportive and symptomatic)	1. Bed rest 2. Liquid or soft low residue diet 3. Antispasmodics if necessary
Restoration and maintenance of fluid and electrolyte balance	1. Adequate fluid intake by mouth if possible 2. Parenteral fluids if necessary
Elimination of etiological agent	1. Antimicrobial therapy with broad-spectrum antibiotics

If bowel evacuations are occurring at frequent intervals the patient's strength may be conserved by the use of absorbent diapers. Abdominal cramps and tenesmus may usually be relieved by the administration of antispasmodics as for example:[10]

	Gm. or ml.
Tr. belladonna	8
Sodium bromide	10
Elixir phenobarbital ad	60

Sig. 1 teaspoonful q. 4 hr.

In severe cases the judicious use of codeine or morphine may be indicated in order to give the patient a few hours' rest at the critical phase of the disease. Purgation is contraindicated since it merely adds insult to an already highly irritated bowel. During the latter stages of convalescence a gradual return to full diet and activity should be carried out.

Fluid and Electrolyte Replacement: Diarrhea of any degree tends to upset fluid and electrolyte balance and in severe cases of bacillary dysentery the loss of these materials may reach significant levels. In the absence of vomiting a liberal intake of fluids by mouth is all that is needed in the milder cases. If the diarrhea is severe and protracted parenteral fluids may be required and this need is intensified by the occurrence of vomiting. Five per cent glucose in physiological saline is the most commonly used preparation; the administration of 1000-2000 ml. daily at the height of the disease will add greatly to the patient's comfort and well being. As in cholera the administration of whole blood or plasma is rarely indicated.

Antimicrobial Therapy: The broad-spectrum antibiotics oxytetracycline (Terramycin), chlortetracycline (Aureomycin) and chloram-

phenicol (Chloromycetin) are all effective in eradicating the bacterial invader. Recent experience[11] in Korea in the treatment of severe bacillary dysentery has shown that these antibiotic agents are effective in surprisingly small amounts: a total of 4 grams over a period of twenty-four hours is the recommended dosage. The most widely used schedule calls for an initial dose of 2 grams, followed by 1 gram at twelve and twenty-four hours. This regime leads to the rapid elimination of organisms from the stools, and nearly all cases are culturally negative within a matter of five or six days. Clinical improvement usually begins within twenty-four hours. As yet the development of drug-resistant strains has presented no significant problem. Of the three agents mentioned, oxytetracycline (Terramycin) appears to be the drug of choice because of its relatively low incidence of undesirable reactions and its marked efficacy in the treatment of amebic dysentery. This last point is important in those cases in which a differential diagnosis cannot be made. Tetracycline (Achromycin), the latest member of this series, has not received extensive clinical trial as yet, but in vitro studies[12] suggest that it would also be effective in the treatment of bacillary dysentery.

During the second World War various sulfonamide compounds were widely employed in therapy of bacillary dysentery. The relatively soluble compounds (notably sulfadiazine) appeared to be the most effective, and at first their administration to patients suffering from the disease resulted in a prompt amelioration of symptoms and a rapid disappearance of the organism from the stools. Unfortunately drug-fast strains soon made their appearance in significant numbers and this tendency on the part of dysentery bacilli to develop resistance to the action of the sulfonamides has limited the usefulness of these drugs as therapeutic weapons.[13] Sulfadiazine is the drug of choice among these compounds; a conservative dosage schedule calls for the administration of 4 grams initially followed by 1 gram every six hours until the patient's bowel movements have been normal for two or three days. It is important to maintain an adequate urinary output (2-3 liters per day) during the course of sulfadiazine therapy in order to obviate the dangers arising from crystalluria.

Diarrheal Disease Caused by Bacterial Food Poisoning

Bacterial food poisoning in the strict sense of the term refers to disease caused by food contaminated with bacteria, or with the products

TABLE IV.—COMPARISON OF INTOXICATION AND INFECTION TYPES OF GASTROENTERITIS

Category	*Intoxication**	*Infection‡*
Pathogenesis	Ingestion of preformed toxin	Multiplication of organism within gut
Incubation period	Brief (1-4 hours)	Longer (12-24 hours)
Duration of symptoms	Brief (hours)	Longer (days)
Vomiting	Severe	Usually not marked
Fever	Usually absent	Usually present
Convalescence	Rapid	More prolonged
Communicability	Non-infectious	Infectious

* As exemplified by staphylococcal enterotoxic gastroenteritis
‡ As exemplified by salmonella gastroenteritis.

of bacterial growth. In some types the predominant symptoms refer principally to the gastrointestinal tract (e.g., vomiting and diarrhea); in others the CNS may be chiefly involved as in botulism. The present discussion will be limited to a consideration of the former conditions.

Diarrhea due to bacterial food poisoning falls into two groups depending upon the pathogenesis of the condition.[3-5] In the first the condition is primarily an *intoxication;* the bacterial organisms multiply in the food before it is ingested and in the process produce noxious substances in such concentration that when the food is consumed nausea, vomiting and diarrhea occur even though multiplication of the organism in the gastrointestinal tract is negligible.

The second group represents essentially a *food infection.* In these circumstances food becomes contaminated with pathogenic organisms which under proper conditions multiply in the food to a greater or lesser degree. Once introduced into the gut by means of this vehicle the organisms establish themselves in the intestinal wall, where they multiply and set up a genuine infection. The course of this infection may be long or short, depending upon a variety of conditions associated with the virulence of the invading organism and the resistance of the host.

It is necessary to emphasize the essential difference between the intoxication and the infection types of gastroenteritis (Table IV). In

the former, preformed toxin is ingested by the host and little or no further toxin is manufactured within the gastrointestinal tract since multiplication of the offending organism, if it occurs at all, does so only in negligible amounts. Hence we find a brief incubation period, an explosive onset, a relatively short period of acute afebrile illness followed by rapid recovery. Furthermore, since no infectious process is set up within the gut wall itself, there is little or no inflammatory reaction in this organ and hence microscopic examination of the diarrheal stools shows an absence of any significant inflammatory exudate. The patient is non-infectious. In contrast, a typical case of food infection shows a longer incubation period, a less abrupt onset of signs and symptoms, some degree of pyrexia and a more prolonged clinical course in all but mild cases, followed by a period of definite convalescence. In these cases microscopic examination of the stools reveals a highly cellular exudate since the gut wall is the seat of an active inflammatory process. The patient is potentially infectious for others for a variable period of time.

From the epidemiological point of view, in instances where bacillary dysentery, cholera and the enteric fevers are transmitted by the vehicle of contaminated food, these diseases should be described as cases of food infection. In actual practice, however, the infection type of food poisoning is usually limited to gastroenteritis caused by food infected with the following organisms: 1) members of the genus Salmonella other than typhoid and paratyphoid bacilli; 2) Streptococcus fecalis; and 3) a variety of gram-negative organisms of which several members of the genus Proteus and certain types of late lactose fermenting coliform bacilli are the most prominent. The important role of the Salmonella in food infections is well recognized as a result of many clinical and laboratory observations. Less well established is the significance of Streptococcus fecalis, while the pathogenic importance of the organisms listed under Group 3 has not been critically assessed as yet.

The commonest type of bacterial food intoxication giving rise to diarrhea is staphylococcal food poisoning, or more accurately, staphylococcal enterotoxic gastroenteritis. Certain strains of this organism produce a heat stable enterotoxin, which if ingested in sufficient amounts gives rise to characteristic symptoms. After a brief incubation period averaging one to four hours there is an explosive onset of nausea and vomiting followed almost immediately by diarrhea and often accompanied by

headache, abdominal pain and prostration. The temperature usually is normal or but slightly elevated. If the vomiting and diarrhea continue for any length of time thirst develops, and in a severe case the patient may go into a state of collapse approaching shock with low blood pressure, rapid pulse and cold clammy skin. As a general rule the acute symptoms rarely last more than six hours and most cases are well on the road to recovery at the end of twenty-four hours. The case fatality rate is practically nil.

The diagnosis of staphylococcal enterotoxic gastroenteritis depends upon a combination of epidemiological and clinical observations supported by pertinent laboratory data.[5] The sudden onset of the typical symptoms among the individual members of a group which one to six hours previously have partaken of one of the foods frequently serving as a vehicle for staphylococci (custards, bakery products, ham, poultry or milk) suggests the diagnosis. Examination of the diarrheal stools reveals an absence of the cellular exudate so characteristic of inflammatory conditions of the bowel. Gross blood is rarely observed and mucus is not conspicuous.

Since the toxin is preformed in the contaminated food prior to its ingestion and there is little or no multiplication of the causative organism in the gut, stool cultures are usually negative. More important is the isolation of significant numbers of staphylococci from the suspected foods. Staphylococcus aureus is a more common offender than Staphylococcus albus and most strains of enterotoxin producing staphylococci are coagulase positive. Phage typing offers a promising method for the further identification of these strains, but as yet this technique is carried out in but a few laboratories. The usual source of the enterotoxin producing staphylococci is a food handler who is carrying the organism either in his nose or in a pustule on his hands. The detection of such a carrier furnishes additional epidemiological evidence supporting the diagnosis.

Since relatively few strains of staphylococci are enterotoxin producers the mere finding of large numbers of these organisms in a suspected food or their isolation from a food handler is no more than suggestive evidence. A far stronger case of the implication of these organisms can be built up if it can be proven that they are in actual fact toxin producers. This is unfortunately difficult to do. Little is known about the specific properties of the enterotoxin, other than that it is re-

markably resistant to the action of heat, a fact which is important in the epidemiology of the disease. There are no reliable laboratory tests available for its detection. Although both kittens and monkeys have been reported to be more or less susceptible to the action of the toxin they appear to be less sensitive than man. In actual fact most of our knowledge concerning the action of the enterotoxin has been obtained by means of experiments involving human volunteers. Although the diagnosis of staphylococcal food poisoning or gastroenteritis is made quite frequently today, the laboratory evidence supporting it is usually circumstantial at best, and in most instances, the diagnosis is made on clinical grounds, either alone or supported by epidemiological data.

As regards therapy it is usually easy to enforce bed rest during the active phase of the disease since the patient is nearly always incapacitated during this period. The patient should be kept warm and as comfortable as possible. The use of antispasmodics is not indicated.

If the vomiting and diarrhea continue for more than a few hours dehydration becomes a serious problem. This is best treated by the intravenous administration of 5 per cent glucose in physiological saline solution. An initial infusion of 2000 ml. may be repeated in three to four hours if the patient's condition has not improved markedly by that time. Rarely is the acid-base equilibrium upset to a point where the administration of base by mouth or vein is necessary. If the patient's blood pressure drops alarmingly the prompt administration of plasma or of a plasma expander is indicated.

Chemotherapy aimed at the elimination of the causative cocci is not necessary since these organisms do not multiply to any appreciable extent in the gastrointestinal tract. No antitoxin is available to neutralize the action of the toxin. Purgation to eliminate the toxin has been recommended. There is, however, no evidence that it does more than offer further insult to an already highly irritable bowel. Bed rest, maintenance of fluid and electrolyte balance and watchful waiting are the cardinal therapeutic points. In the great majority of cases the acute phase of the disease lasts but a few hours, and recovery is swift and complete.

The acute gastroenteritis of staphylococcal origin which occasionally develops during the course of therapy with the broad-spectrum antimicrobial agents (usually chlortetracycline, oxytetracycline or chloramphenicol) is presumably an infection rather than an intoxication.[2]

TABLE V.—SALMONELLA, TYPES MOST FREQUENTLY ISOLATED FROM CASES OF GASTROENTERITIS IN MAN (U.S.A.)

Rank	*Type*	*Antigenic Group*	*Chief Animal Reservoir*
1	S. typhi murium	B	Rodents
2	S. newport	C_2	Poultry
3	S. oranienburg	C_1	Poultry
4	S. cholerae suis	C_1	Swine
5	S. anatum	E	Poultry
6	S. montevideo	C_1	Poultry
7	S. panama	D	Undetermined

Although hemolytic coagulase positive Staphylococcal aureus may be isolated in practically pure culture from the fecal discharges of these patients, there is as yet no evidence suggesting that these organisms are necessarily enterotoxin producers. Furthermore the liquid stools contain large amounts of pus and mucus, thus suggesting that the process is essentially an inflammatory one. The presumed course of events in this condition is first a change in the normal bacterial flora of the bowel as a result of the antimicrobial therapy followed by emergence of a drug-fast strain of Staphylococcus aureus which multiplies practically unhindered in the gut in the comparative absence of other bacteria. The diarrheal process is usually severe and dehydration and prostration develop with alarming rapidity. Therapy must be vigorous in order to prevent a fatal outcome. Parenteral fluid (5 per cent glucose in physiological saline) should be administered promptly, and this should be supplemented with plasma if there are any signs of impending shock. The administration of whole blood is indicated if there is evidence of significant loss of blood into the bowel. Antimicrobial therapy should be discontinued until the sensitivity spectrum of the organism has been determined. In instances where sensitivity to another antimicrobial agent (e.g., erythromycin) may be demonstrated, therapy with it should be initiated.

So-called food poisoning due to infection with various members of the genus Salmonella, or more scientifically, salmonella gastroenteritis, is an important cause of diarrheal disease. Although a large number of

Salmonella types have been implicated as causative agents, the seven most important (in the descending order of frequency) in the United States[5] are S. typhi murium, S. newport, S. oranienburg, S. cholerae suis, S. anatum, S. montevideo and S. panama (Table V); of these the first (S. typhi murium) is reported to be isolated from 30-40 per cent of all outbreaks of salmonella gastroenteritis occurring in the U.S.A. and Canada. These organisms are fundamentally parasites of lower animals, and man frequently becomes infected by the ingestion of tissue (meat, poultry) or of eggs and dairy products derived from infected animals. Since rats and mice are frequently infected with S. typhi murium, and may excrete these organisms in large numbers in their urine and feces, foodstuffs may become contaminated in this way if rodents have access to them. Once infected with these organisms, man may continue to excrete them for an appreciable length of time, and thus may himself serve as an effective means of spread. The salmonella species limited largely to man (the typhoid and paratyphoid bacilli) are far more likely to cause enteric fever than gastroenteritis.

Although most authorities agree that salmonella gastroenteritis is primarily due to an infectious process involving the intestinal tract and that the multiplication of organisms in the gut wall is responsible for the development of the typical clinical picture, it has been suggested from time to time that diarrhea may occur as a result of the ingestion of toxic bacterial products without the establishment of a true infectious process in the gut itself. There is, however, no direct experimental evidence supporting this view that diarrhea may occur as a result of salmonella intoxication.[5]

The usual incubation period lies between twelve and twenty-four hours, thus supporting the hypothesis that the process is a bacterial infection in which the organisms in the gut must multiply to reach some critical number before symptoms are produced. The onset tends to be abrupt; cramping abdominal pain, diarrhea and headache are the commonest complaints. Nausea and vomiting do occur in a fair proportion of cases, but are rarely severe or protracted. Fever is nearly always present. The stools, foul smelling at first, rapidly become liquid. Although the finding of gross blood is a rare occurrence, microscopic examination reveals the characteristic inflammatory exudate.

Although the diagnosis of salmonella gastroenteritis may be suspected on the basis of clinical and epidemiological grounds the final

diagnosis requires the use of the laboratory. The relatively longer incubation period, the presence of fever and constitutional symptoms and the fact that vomiting, if present in the early stages, is rarely excessive, serves to differentiate it from staphylococcal food poisoning. On the other hand the symptomatology of salmonella gastroenteritis closely resembles that of bacillary dysentery and microscopic examination of the stools reveals the characteristic polymorphonuclear exudate in both instances. This is in contrast to the mononuclear exudate of amebic dysentery, and to the absence of any inflammatory exudate in the case of staphylococcal food poisoning.

A firm diagnosis of salmonella food infection requires that the same type of Salmonella be isolated from the suspected food and from the stools of a significant proportion of the individuals suffering from the disease. In actual practice this is rarely accomplished, for almost invariably the suspected food or foods will be found to have been eaten or discarded by the time epidemiological investigations are initiated. A positive stool obtained from an individual presenting the typical clinical picture offers strong presumptive evidence in favor of the diagnosis. If the same organism is isolated from a significant proportion of all the individuals stricken at the same time, the evidence is all the stronger.

The isolation and identification of the organism in the laboratory requires several steps.[14] The stool or rectal swab is cultured in an enrichment medium such as tetrathionate broth which after twenty-four hours is then streaked out on a selective medium (such as shigella-salmonella agar) which inhibits the growth of non-pathogenic organisms. Suspicious colonies are carried through various biochemical tests and are identified as members of the salmonella group by means of agglutination tests employing salmonella grouping sera. These procedures are routine ones for any well-equipped hospital or health department laboratory. The final identification of the actual Salmonella species requires the use of delicate serological techniques to identify the somatic and flagellar antigens of the suspected organism.These procedures are carried out only in specialized laboratories such as the Salmonella Typing Center at the Communicable Disease Center of the U. S. Public Health Service in Atlanta, Georgia.

The therapy of salmonella gastroenteritis consists *first* of general supportive measures such as bed rest and liquid diet during the acute phase of the disease, and *second* of the restoration and maintenance of

fluid and electrolyte balance. The loss of these substances is rarely as great in this condition as in staphylococcal food poisoning or in bacillary dysentery and in the case of average severity fluids may be taken by mouth in sufficient quantities to maintain the physiological balance. Occasionally the administration of parenteral fluids is required; it is rare, however, that more than one or two infusions of 5 per cent glucose in physiological saline are necessary. At the moment there is available no specific antimicrobial therapy which is effective in eradicating the causative organism. Chloramphenicol (Chloromycetin), used with success in the therapy of acute typhoid fever, has yielded disappointing results in the treatment of gastroenteritis due to other members of the salmonella group. In the great majority of instances the infectious process is a self-limited one and complete clinical recovery within a matter of one to two weeks is the general rule. Occasionally the patient becomes a chronic carrier of the offending organism; as such he continues to be a public health danger as long as he continues to shed the organism. Very rarely the organism invades the blood stream with the subsequent development of a septicemic state, a most serious complication. The case mortality rate for the uncomplicated disease is practically nil except in the very young and in the aged.

Prevention of Acute Diarrheal Disease of Bacterial Origin

The effective prevention of acute diarrheal disease of bacterial origin is primarily a problem of public health. The maintenance of adequate standards of environmental sanitation, the safeguarding of food and water supplies from fecal pollution, the proper inspection of meat, poultry and dairy products before their release for public consumption and the regulation and examination of public food handlers are all measures involving the public health authorities rather than the individual practicing physician. The absence of effective immunization procedures in any of the diseases discussed in detail in the present paper makes it all the more imperative that these relatively non-specific measures should be carried out with diligence and persistence.

The role of the individual physician in the prevention of these conditions is not inconsequential nonetheless. Perhaps his most important contribution lies in the prompt diagnosis, isolation and treatment of cases of infectious diarrhea, thus reducing the chance of spread to other individuals. He can do much to impress the lay public with the

importance of maintaining high standards of personal hygiene. Further, he is in a favorable position to educate the public as to the simple effective measures available for the prevention of gastroenteritis due to staphylococcal enterotoxin. Here emphasis on the personal hygiene of food handlers, the proper cooking of foods and the necessity of adequate refrigeration during the period intervening between preparation and consumption of foods which are particularly conducive to the growth of staphylococci may play an important role in reducing the incidence of the disease. And finally, the practicing physician must remain acutely conscious of the potential hazards of therapy with the so-called broad-spectrum antimicrobial agents.

REFERENCES

1. Jordan, W. S., Jr., Gordon, I. and Dorrance, W. R. A study of illness in a group of Cleveland families; transmission of acute non-bacterial gastroenteritis to volunteers; evidence for two different etiologic agents, *J. exp. Med. 98:* 461-75, 1953.
2. Finland, M. and Weinstein, L. Complications induced by antimicrobial agents, *New Engl. J. Med. 248:*220-26, 1953.
3. Dack, G. M. *Food poisoning.* Chicago, University of Chicago Press, 1949.
4. Dewberry, E. B. *Food poisoning.* 3.ed. London, Leonard Hill, Ltd., 1950.
5. Meyer, K. F. Medical progress: Food poisoning, *New Engl. J. Med. 249:*765-72; 804-12; 843-51, 1953.
6. Neter, E., Webb, C. R., Shumway, C. N. and Murdock, M. R. Study on etiology, epidemiology and antibiotic therapy of infantile diarrhea, with particular reference to certain serologic types of Escherichia coli, *Amer. J. publ. Hlth. 41:*1490-96, 1951.
7. Smith J. The association of serological types of Bacterium coli with infantile gastro-enteritis, *J. Path. Bact. 66:*503-11, 1953.
8. Hardy, A. V., Mason, R. P., Hamerick, D. and Mitchell, R. B. The bacteriologic diagnosis of enteric infections, *U.S. Armed Forces med. J. 4:*541-53, 1953.
9. Hardy, A. V., Watt, J. and DeCapito, T. M. Studies of the acute diarrheal diseases; new procedures in bacteriological diagnosis, *Publ. Hlth. Rep. 57:*521-24, 1942.
10. Thompson, C. M., White, B. V., Jr., and Schafer, W. L. Shigellosis studies; etiology and clinical features, *U.S. Nav. med. Bull. 46:*528-40, 1946.
11. Hardy, A. V., Mason, R. P. and Martin, G. A. The antibiotics in acute bacillary dysentery, *Ann. N. Y. Acad. Sci. 55:* 1070-74, 1952.
12. Finland, M., Purcell, E. M., Wright, S. S., Love, B. D., Jr., Mou, T. W. and Kass, E. H. Clinical and laboratory observations of a new antibiotic, tetracycline, *J. Amer. med. Assoc. 154:*561-68, 1954.
13. Cheever, F. S. The treatment of shigellosis with antibiotics, *Ann. N. Y. Acad. Sci. 55:*1063-69, 1952.
14. Galton, M. M., Hardy, A. V. and Mitchell, R. B. The public health laboratory diagnosis of enteric infections, *Amer. J. trop. Med. 30:*77-90, 1950.

HISTOPLASMOSIS*

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HISTOPLASMOSIS was first recognized and reported in Panama in 1906 by Dr. Samuel T. Darling,[1, 2] who named the fungus Histoplasma capsulatum in the mistaken belief that it was a protozoon. Concepts of the disease and its causal agent have undergone several changes since that time. Da Rocha-Lima[3] corrected the error concerning the taxonomic position of the organism when he expressed his belief that Histoplasma was not a protozoon but a fungus. De Monbreun[4] conclusively proved the fungus nature of the organism by obtaining cultures from the first case in which an antemortem diagnosis was made (Dodd and Tompkins[5]), and by reproducing the disease in monkeys by experimental injection of a culture. The specific name, capsulatum, also has long been recognized as a misnomer. The appearance in sections of a capsule is actually an artefact caused by shrinkage of a vacuolate cytoplasm. Whatever extracellular capsular material this moist yeast-like fungus has is inconspicuous and, indeed, inapparent in histologic preparations. Despire these etymologic objections to the name the binomial Histoplasma capsulatum is valid and fortunately it has remained stable in a field of biology where there have been many nomenclatorial changes. Finally, the concept of histoplasmosis as a rare, invariably fatal disease has given place to the recognition that most cases are subclinical or mild.

Histoplasmosis is a systemic mycosis of man and animals caused by the dimorphic fungus, Histoplasma. Its outstanding characteristic, as DeMonbreun[4] pointed out when he proposed changing its name to "cytomycosis of Darling," is "a generalized infection of the reticuloendothelial system with the occurrence and probable proliferation of the parasitic form of the fungus within these cells." Its predilection for the reticuloendothelial system and the intracellular habit of the

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fungus differentiate it from most mycoses, although it is indistinguishable in tissues from epizootic lymphangitis of horses.[6]

An excellent summary of the characteristics of histoplasmosis, as then known, was prepared in 1945 by Parsons and Zarafonetis.[7] They reviewed seventy-one cases and it is notable that only four of these were surviving at the time of the report. Austria, British Honduras, East Java, England, Mexico, the Philippines and Rhodesia each supplied one case; Argentina, two cases; Brazil and Panama Canal Zone, three cases each and the United States fifty-six cases. In this series there was a high peak incidence in infants with a second low peak occurring in the fifth, sixth and seventh decades of life. There was no sex differential below the age of ten years, but of the patients over ten years, there were forty-three males and six females. The authors suggested that this difference may be due to differences in exposure to a fungus in nature.

In this series fever was present in forty-seven of forty-nine cases; hypochromic anemia in forty-four of forty-six, hepatomegaly in thirty-nine of fifty-one, splenomegaly in thirty-seven of fifty-one, lymphadenopathy in twenty-nine of forty-two, leukopenia in twenty-eight of forty-eight, albuminuria in twenty-four of thirty-seven, pulmonary lesions in thirty-four of sixty-one, gastrointestinal tract lesions in twenty-eight of sixty-one, emaciation in nineteen of sixty-one, and ulcerative lesions of the oropharynx in twenty-one of sixty-one. Adrenal lesions were reported in eighteen cases, and ulcerative or papular skin lesions, renal lesions, vegetative endocarditis, and lesions of the brain, pancreas, thymus and eye occurred less frequently. The reporting of many additional cases has done little to change this picture of disseminated, fatal histoplasmosis. If some of the rarer manifestations of this mycosis seem to have been emphasized by presentation as case reports in recent papers it is probably because of their rarity.

Two reports[8, 9] that there is a frequent form of histoplasmosis involving the appendix and mesentery must be discounted. In one of these studies bodies identified as Histoplasma were found in over 10 per cent of 436 appendixes surgically removed from children under sixteen years of age. In the other a 5 per cent incidence of histoplasmosis in appendicitis and a 43 per cent incidence in mesenteric adenitis was reported. Intracellular bodies shown in a photomicrograph of a section are more easily interpreted as nuclear debris and conidia shown in another illus-

tration are obviously spores of some other fungus, probably Aspergillus or Scopulariopsis, and not the large distinctive macroconidia of Histoplasma. Christopherson, Miller and Kotcher[10] were unable to confirm the common occurrence of appendiceal histoplasmosis and C. F. T. Mattern and the author, in a series of 500 appendixes, found no histologic or cultural evidence of histoplasmosis. Our study has not yet been reported.

Case reports made since the valuable paper by Parsons and Zarafonetis have widened the known geographic distribution of histoplasmosis. Mochi and Edwards,[11] in a survey of the world literature of histoplasmosis and histoplasmin sensitivity, mentioned additional cases from Canada, Anglo-Egyptian Sudan, Australia, Bulgaria, Columbia, French Sudan, Hawaii, the Netherlands (with possible exposure in the Dutch East Indies), Portugal, Spain, Turkey, Union of South Africa and Uruguay. I emphasize this wide geographic distribution of histoplasmosis deliberately because the opinion has been current and formally expressed in medical literature that histoplasmosis is a disease principally limited to eastern central United States, with only a rare case in Central or South America and a few other areas.

The actual number of cases of fatal histoplasmosis is not accurately known. Most of the reported cases are from the United States but these reports represent only a part of the actual cases. Undoubtedly lack of adequate laboratory facilities and of awareness of the disease limit the number of diagnoses in many geographic areas and it is well known that within the United States relatively few of the recently diagnosed cases appear as published case reports. In Vital Statistics of the United States for 1950[12] histoplasmosis accounts for forty-four of the 411 deaths reported as due to mycoses in that year. Unfortunately deaths from histoplasmosis were not listed separately for earlier years and reports for more recent years are not yet available.

At the time Parsons and Zarafonetis reported their study one might have stopped at this point in a discussion of the clinical aspects of histoplasmosis. Today the picture is very different. Despite the high mortality rate of disseminated histoplasmosis and the lack of any effective chemotherapy, medical interest in the disease now centers around benign pulmonary histoplasmosis, its differentiation from other pulmonary infections which it mimics, its relationships to pulmonary calcification and histoplasmin sensitivity, and the environmental factors which influence

the occurrence and geographic distribution of Histoplasma. I shall briefly outline the development of this new concept before defining the benign form of histoplasmosis.

A lack of correlation in eastern central United States between pulmonary calcification and tuberculin sensitivity or clinical course of the pulmonary lesion has long been known. In 1930 Sayers and Meriwether[13] reported a study of 125 cases of a "Miliary lung disease due to unknown cause" in miners in Picher, Oklahoma. They suggested that Aspergillus might be the cause of this disease. With the increased application of tuberculin testing and mass x-ray surveys to tuberculosis case finding programs it became more apparent that many persons with pulmonary calcification are not sensitive to tuberculin. Gass and his associates[14] called attention to this discrepancy in Tennessee. Lumsden, Dearing and Brown[15] confirmed this observation in the same area and Olson, Wright and Nolan[16] described the same phenomenon in Ross County, Ohio, suggesting Ascaris as a possible etiologic agent. Smith[17] suggested that nontuberculous calcification in this part of the United States might be due to histoplasmosis.

In 1945 Christie and Peterson[18] reported studies they had been conducting in Tennessee which showed an association between the presence of nontuberculous pulmonary calcification and sensitivity to histoplasmin. In subsequent papers[19, 20] they presented additional evidence on this point. In 1945 and 1946 Palmer[21, 22] reported a remarkable difference in histoplasmin sensitivity and nontuberculous pulmonary calcification among student nurses from different parts of the United States. In 1948 Edwards, Lewis and Palmer[23] related histoplasmin sensitivity to pulmonary calcification in the individuals making up this group of 12,803 student nurses. Sontag and Allen[24] and Furcolow, Mantz and Lewis[25] similarly related histoplasmin sensitivity and pulmonary calcification. Bunnell and Furcolow[26] and Furcolow[27] reported series of cases of histoplasmosis, some of which were benign and were proved by isolation of Histoplasma in culture, and these were forerunners of many later similar reports.

This rapidly changing concept of histoplasmosis depended entirely in the beginning upon the use and interpretation of the intradermal test with histoplasmin. The histoplasmin used in most of the early studies, like other histoplasmins used to date, was non-specific. There is a strong cross reaction with blastomycosis (even in dilutions as high as 1:10,000)

and to a lesser degree with other mycoses.[28] The reciprocal cross reaction occurs but is usually less marked because most strains of Blastomyces produce a less potent antigen than does Histoplasma. The occurrence of an antigen common to Histoplasma and Blastomyces has been observed by others who have looked for it.[29-31]

This nonspecificity of histoplasmin inevitably makes interpretation of a skin reaction somewhat equivocal. To date, however, the results of cultures from the type of benign pulmonary disease in question seem to have justified the early assumption that histoplasmin sensitivity can usually be equated with histoplasmosis. If Blastomyces or another common pathogenic fungus is responsible for part of the nontuberculous pulmonary calcification it has not been isolated in culture as yet. The etiology in cases of pulmonary calcification in individuals who do not react to either tuberculin or histoplasmin has not been determined.[24, 32]

Benign histoplasmosis has emerged, then, as an acute pneumonitis characterized by fever, malaise, weight loss and adenopathy. The pulmonary lesions may resolve or they may calcify. One or more of these signs and symptoms may be mild or may even be lacking and if one accepts histoplasmin sensitivity as diagnostic proof of a past infection, histoplasmosis may in fact be quite inapparent. In many areas 80 per cent of general population groups react to histoplasmin and sensitivity appears early in the preschool and school groups. Close observation of a group of preschool or young school children and a search of their medical histories may fail to reveal an episode which explains the acquisition of histoplasmin sensitivity.[32] Demonstrable circulating antibodies against Histoplasma are usually lacking in these children. Aside from its nonspecificity it is obvious that histoplasmin has little value as a diagnostic tool in a community where most of the population have been histoplasmin positive since early childhood.

Serologic tests may be more helpful than intradermal tests if there is clinical illness and if a rise in complement fixing antibody titer can be demonstrated. One is still dependent, however, upon an antigen which is nonspecific, and not all patients with proved histoplasmosis have a detectable antibody titer. Although references to use of serologic methods occur in some of the early papers on histoplasmosis one of the earliest systematic attempts to standardize the complement fixation test is that of Tenenberg and Howell.[33] Their technique, utilizing histoplasmin as an antigen, was applied to the examination of a considerable series of human

sera. The use of a yeast-phase antigen seems to offer some advantages and is used by many laboratories.[34-36]

A third diagnostic procedure is the histologic demonstration of Histoplasma in a tissue obtained at biopsy or autopsy or in pathological secretions. The productivity of this method has been greatly increased by the application of the periodic acid-Schiff stain.[37, 38] This selective stain greatly increases the ease with which one can locate a few isolated cells of Histoplasma which would be missed in a hematoxylin-eosin stain. The histopathologic diagnosis of histoplasmosis is usually acceptable in a typical case of disseminated histoplasmosis. In an occasional case, because of variation in size of Histoplasma and its resemblance to other fungi the diagnosis may be equivocal. Differentiation in tissue from H. farciminosum in epizootic lymphangitis of horses is impossible. The two fungi are alike in size, shape, staining reaction and intracellular position. Histoplasma may be confused also with Blastomyces dermatitidis because of variations in size of both fungi.[39-41] This resemblance is increased in the case of H. duboisii, a species described from African cases of histoplasmosis in which large forms of Histoplasma are commonly present in tissues.[42] Layton, McKee and Stamler[43] reported a case of dual infection proved by culture of both fungi and I believe such cases will be recognized in greater numbers if extensive culture studies are made. The fallibility of a histopathologic diagnosis is further increased by the ability of Torulopsis glabrata and perhaps other yeasts to mimic the morphology and intracellular habit of Histoplasma.[44]

The conclusive diagnostic criterion one would like to obtain in each case is isolation of the fungus, Histoplasma capsulatum, in culture. This usually presents no serious problem in the disseminated disease. Histoplasma can be isolated by inoculating a slant of Sabouraud's agar or other medium with blood, bone marrow, an excised lymph node, the exudate from a mucous membrane ulcer, or sputum. If the inoculum is contaminated, growth of bacteria can be inhibited by addition of penicillin and streptomycin to the medium at the level of 25-100 units of each per ml. of agar. In the case of sputum, where Candida or inhaled fungus spores may also contaminate the material, it should be injected intraperitoneally into mice. The mice should be killed after four weeks and cultures made from the liver and spleen.

The isolation of Histoplasma from the acute benign form of histoplasmosis is more difficult. Bone marrow or blood cultures should be

made but are seldom successful. Cultures should be made from excised lymph nodes and mice should be inoculated with sputum and stomach washings.

In attempts to isolate Histoplasma cultures should be incubated at room temperature or at 30°C. Isolation at 37°C may be successful but is not dependable. When Histoplasma grows at room temperature it is a white to brown mold which bears two types of spores, microconidia which are spherical, 3-4μ in diameter and minutely spiny; and macroconidia which are spherical or rarely clavate, 8-12μ in diameter with finger-like appendages rather evenly spaced over the surface. Like most of the fungi causing systemic mycoses, Histoplasma is dimorphic. When these conidia from the saprophytic growth phase are introduced into a mammalian host they give rise at once to the parasitic phase which is yeast-like. These cells are egg-shaped and are usually 2-3 x 3-4μ in size, although larger forms are sometimes found, as previously noted. They reproduce by budding at the smaller end, and they are characteristically located within macrophages.

The epidemiology of histoplasmosis is that of an infectious but non-contagious disease, varying greatly in severity, and in which the source of infection appears to be a mold growing as a saprophyte in soil without necessary relationship to another person or animal. Evidence for the non-contagious nature of histoplasmosis rests upon failure to observe direct transmission from patient to contacts except under unusual circumstances and lack of spread from animal to animal when normal and experimentally infected animals are caged together. In the rare instances when two or more members of a household have had disseminated histoplasmosis it has been impossible to rule out the factor of a common environmental exposure. This factor can not be excluded either in the case of histoplasmosis in dogs sharing an outside run or kept in adjacent pens. Normal mice kept in a battery jar with infected mice remain uninfected. This is surprising in view of the high susceptibility of the mouse to infection by a single fungus cell via the intraperitoneal route. The yeast-like phase of Histoplasma is infectious under experimental conditions but it does not appear to be effective in direct transmission of the disease.

The term "histoplasmosis epidemic" refers not to an epidemic spread but to cases of histoplasmosis in a group of persons having a common exposure. Loosli and associates[45, 46] have reported a very thorough study

of a small family epidemic in which the fungus was isolated in culture from one of the patients and repeatedly over a period of years from a silo which was apparently the source of infection. Other so-called epidemics of histoplasmosis have been related to exposure in caves, storm cellars, an old water tower, and old buildings. Grayston and Furcolow have investigated and reviewed several of these episodes.[47, 48] They identified these outbreaks of pneumonitis as histoplasmosis by the following criteria: "1) isolation of *Histoplasma capsulatum* from the soil of the point source of the epidemic, 2) positive serological tests for histoplasmosis, 3) positive histoplasmin skin tests, 4) development of miliary calcification in the lungs." In most of these studies the diagnosis was made retrospectively and the authors isolated Histoplasma from soil at one site of an epidemic as long as nine years after the episode.

It is apparent from these considerations that the epidemiology of histoplasmosis is determined by the saprophytic occurrence of Histoplasma in-soil and exposure of a susceptible population. The actual isolation of Histoplasma from soil was first reported in 1949.[49] Isolations were made during the course of a systematic search for saprophytic sources of the fungus. A wide variety of materials such as soil and dust from basements, moldy cereal grains, chaff and dust from barn and mow floors, well rotted manure and soil from barnyards were examined. The first isolation was from red clay soil taken from under the edge of a chicken house. Subsequent sampling in this and other studies have shown an association between the occurrence of Histoplasma in soil and the presence of chickens.[50-52] Ajello et al.[52] were first to report this association. Their paper is further notable because the reported isolation of Histoplasma from soil was the first isolation of Histoplasma from any source in Williamson County, Tennessee, an area where 70 per cent of the population react to histoplasmin, but where, at that time, no human cases of histoplasmosis had yet been diagnosed.

Histoplasma can not be isolated in direct culture easily from soil because of the rapid overgrowth in culture of other saprophytic fungi, and it is not practicable to attempt direct isolations. It can be done easily by the simple expedient of suspending the soil sample in physiological saline and injecting the supernatant into mice. The mouse, although infected, does not die of histoplasmosis. It should be killed one month later and cultures should be made from the liver and spleen. The effectiveness of this method depends upon the high susceptibility of the mouse to

histoplasmosis and its ability to destroy nonpathogenic organisms in the soil, which in a direct culture would rapidly overgrow Histoplasma. Ajello and Runyon[53] have shown that a single macroconidium of Histoplasma injected intraperitoneally will infect the mouse, and Rowley and Huber[54] have demonstrated that 1-10 viable yeast-like cells are also infective.

The ability of a single spore of Histoplasma to infect a mouse when injected intraperitoneally greatly increases the sensitivity of the method used for isolation of the fungus from soil, but it also greatly increases the danger of error. If the technique is used in a laboratory where the occurrence of laboratory infections of clinical severity indicates a heavy contamination of the laboratory air it is obvious that the method may give erroneous results. If, in the examination of a soil sample, a mouse is injected with a soil suspension containing a single spore it may develop histoplasmosis. However this spore may have been in the sample when collected or it may have blown into the sample at any stage of the procedure after it was brought to the laboratory. It is therefore important that this technique be used only with caution and a realization of the possibility of error.

Histoplasmosis occurs in many species of animals[55] reaching an incidence of 50 per cent in cats and dogs as proved by isolation of Histoplasma in culture from hilar lymph nodes of essentially healthy animals.[56, 57] This frequent occurrence of histoplasmosis in animals has provided another productive method of investigating the geographic distribution of the disease.

The conditions which determine the wide geographic and the spotty local distribution of Histoplasma in soil have not yet been fully delineated. Neither is it apparent why histoplasmosis occurs throughout the world (having been reported from twenty-four countries) while prevalent histoplasmin sensitivity has such an irregular and limited geographic distribution. Interest in this disease, which does not respond to any presently safe and available chemotherapeutic agent, which is responsible for 10 per cent of the mycotic deaths reported in the United States, and which presents one of the most important problems in the differential diagnosis of pneumonitis, may be expected to stimulate further investigations leading to eventual answers.

(REFERENCES ON NEXT PAGE)

REFERENCES

1. Darling, S. T. A protozoon general infection producing pseudotubercles in the lungs and focal necroses in the liver, spleen and lymph nodes, *J. Amer. med. Assoc. 49:*1283-85, 1906.
2. Darling, S. T. The morphology of the parasite (Histoplasma capsulatum) and the lesions of histoplasmosis, a fatal disease of tropical America, *J. exp. Med. 11:*515-34, 1909.
3. da Rocha-Lima, H. Beitrag zur Kenntnis der Blastomykosen; Lymphangitis epizootica und Histoplasmosis, *Cbl. Bakt.* Abt. 1, *67:*233-49, 1912.
4. DeMonbreun, W. A. The cultivation and cultural characteristics of Darling's Histoplasma capsulatum, *Amer. J. trop. Med. 14:*93-125, 1934.
5. Dodd, K. and Tompkins, E. H. A case of histoplasmosis of Darling in an infant, *Amer. J. trop. Med. 14:*127-37, 1934.
6. Conant, N. F. A cultural study of the life-cycle of Histoplasma capsulatum Darling 1906, *J. Bact. 41:*563-79, 1941.
7. Parsons, R. J. and Zarafonetis, C. J. D. Histoplasmosis in man; report of seven cases and a review of seventy-one cases, *Arch intern. Med. 75:*1-23, 1945.
8. Raftery, A., Trafas, P. C. and McClure, R. D. Histoplasmosis; a common cause of appendicitis and mesenteric adenitis, *Ann. Surg. 132:*720-28, 1950.
9. Raftery, A. Subclinical histoplasmosis; gastrointestinal histoplasmosis of children, *J. Amer. med. Assoc. 145:*216-19, 1951.
10. Christopherson, W. M., Miller, M. P. and Kotcher, E. Examination of human appendixes for Histoplasma capsulatum, *J. Amer. med. Assoc. 149:* 1648-49, 1952.
11. Mochi, A. and Edwards, P. Q. Geographical distribution of histoplasmosis and histoplasmin sensitivity, *Bull. World Hlth. Org. 5:*259-91, 1952.
12. United States National Office of Vital Statistics. *Vital statistics of the United States, 1950,* v *3,* p. 62.
13. Sayers, R. R. and Meriwether, F. V. Miliary lung disease due to unknown cause, *Publ. Hlth. Rep. 45:*2994-3009, 1930.
14. Gass, R. S. et al. Tuberculosis studies in Tennessee; roentgenological evidence of tuberculosis infection in relation to tuberculin sensitivity in school children, *Amer. Rev. Tubere. 38:*441-47, 1938.
15. Lumsden, L. L., Dearing, W. P. and Brown, R. A. Questionable value of skin testing as a means of establishing an epidemiological index of tuberculous infection, *Amer. J. publ. Hlth. 29:*25-34, 1939.
16. Olson, B. J., Wright, W. H. and Nolan, M. O. An epidemiological study of calcified pulmonary lesions in an Ohio county, *Publ. Hlth. Rep. 56:*2105-26, 1941.
17. Smith, C. E. Coccidioidomycosis, *Med. Clin. N. Amer. 27:*790-807, 1943.
18. Christie, A. and Peterson, J. C. Pulmonary calcification in negative reactors to tuberculin, *Amer. J. publ. Hlth. 35:* 1131-47, 1945.
19. Christie, A. and Peterson, J. C. Histoplasmin sensitivity, *J. Pediat. 29:*417-32, 1946.
20. Christie, A. Histoplasmosis and pulmonary calcification — geographic distribution, *Amer. J. trop. Med. 31:*742-52, 1951.
21. Palmer, C. E. Nontuberculous pulmonary calcification and sensitivity to histoplasmin, *Publ. Hlth. Rep. 60:*513-20, 1945.
22. Palmer, C. E. Geographic differences in sensitivity to histoplasmin among student nurses, *Publ. Hlth. Rep. 61:*475-87, 1946.
23. Edwards, L. B., Lewis, I. and Palmer, C. E. Studies of pulmonary findings and antigen sensitivity among student nurses; pulmonary infiltrates and mediastinal adenopathy observed among student nurses at the beginning of training, *Publ. Hlth. Rep. 63:*1569-1600, 1948.
24. Sontag, L. W. and Allen, J. E. Lung calcifications and histoplasmin-tuberculin skin sensitivity, *J. Pediat. 30:*657-67, 1947.
25. Furcolow, M. L., Mantz, H. L. and Lewis, I. The roentgenographic appear-

ance of persistent pulmonary infiltrates associated with sensitivity to histoplasmin, *Publ. Hlth. Rep. 62*:1711-18, 1947.

26. Bunnell, I. L. and Furcolow, M. L. A report on ten proved cases of histoplasmosis, *Publ. Hlth. Rep. 63*:299-316, 1948.
27. Furcolow, M. L. Further observations on histoplasmosis; mycology and bacteriology, *Publ. Hlth. Rep. 65*:965-94, 1950.
28. Emmons, C. W., Olson, B. J. and Eldridge, W. W. Studies of the role of fungi in pulmonary disease; cross reactions of histoplasmin, *Publ. Hlth. Rep. 60*:1383-94, 1945.
29. Howell, A., Jr. Studies of fungus antigens; quantitative studies of cross-reactions between histoplasmin and blastomycin in guinea pigs, *Publ. Hlth. Rep. 62*:631-51, 1947.
30. Cross, F. W. and Howell, A., Jr. Studies of fungus antigens; preliminary report on the isolation of an immunologically active polysaccharide from histoplasmin, *Publ. Hlth. Rep. 63*:179-83, 1948.
31. Salvin, S. B. The serologic relationship of fungus antigens, *J. Lab. clin. Med. 34*:1096-1104, 1949.
32. Olson, B. J., Bell, J. A. and Emmons, C. W. Studies on histoplasmosis in a rural community, *Amer. J. publ. Hlth. 37*:441-49, 1947.
33. Tenenberg, D. J. and Howell, A., Jr. A complement fixation test for histoplasmosis; technic and preliminary results on animal sera, *Publ. Hlth. Rep. 63*:163-68, 1948.
34. Salvin, S. B. Complement fixation studies in experimental histoplasmosis, *Proc. Soc. exp. Biol. Med. 66*:342-45, 1947.
35. Campbell, C. C., Saslaw, S. and Knibb, B. S. The use of yeast phase antigens in a complement fixation test for histoplasmosis; results with ground antigens, *J. Lab. clin. Med. 33*:1207-11, 1948.
36. Grayston, J. T. A study of the complement fixation reaction in histoplasmosis, *J. Lab. clin. Med. 40*:90-101, 1952.
37. Lillie, R. D. Reactions of various parasitic organisms in tissues to the Bauer, Feulgen, Gram and Gram-Weigert methods, *J. Lab. clin. Med. 32*:76-88, 1947.
38. Kligman, A. M., Mescon, H. and DeLamater, E. D. The Hotchkiss-McManus stain for the histopathologic diagnosis of fungus diseases, *Amer. J. clin. Path. 21*:86-91, 1951.
39. Tuttle, J. G., Lichtwardt, H. E. and Altshuler, C. H. Systemic North American blastomycosis; report of a case with small forms of Blastomycetes, *Amer. J. clin. Path. 23*:890-97, 1953.
40. Schwarz, J. Giant forms of *Histoplasma capsulatum* in tissue explants, *Amer. J. clin. Path. 23*:898-903, 1953.
41. Binford, C. H. Histoplasmosis; tissue reactions and morphologic variations of the fungus, *Amer. J. clin. Path. 25*:25-36, 1955.
42. Vanbreuseghem, R. Histoplasma duboisii and African histoplasmosis, *Mycologia 45*:803-16, 1953.
43. Layton, J. M., McKee, A. P. and Stamler, F. W. Dual infection with Blastomyces dermatitidis and Histoplasma capsulatum, *Amer. J. clin. Path. 23*:904-13, 1953.
44. Artagaveytia-Allende, R. C. Contribucion al conocimiento de Torulopsis glabrata (Anderson 1917) Lodder y de Vries 1938, *An. Fac. Med. Montevideo 37*:467-69, 1952.
45. Loosli, C. G., Grayston, J. T., Alexander, E. R. and Tanzi, F. Epidemiological studies of pulmonary histoplasmosis in a farm family, *Amer. J. Hyg. 55*:392-401, 1952.
46. Loosli, C. G. et al. Pulmonary histoplasmosis in a farm family; a three-year follow-up, *J. Lab. clin. Med. 43*:669-95, 1954.
47. Grayston, J. T. and Furcolow, M. L. Acute febrile illness with disseminated pulmonary infiltrations; a syndrome caused by Histoplasma capsulatum, *Tuberculology 12*:9-14, 1952.
48. Grayston, J. C. and Furcolow, M. L. The occurrence of histoplasmosis in epidemics—epidemiological studies, *Amer. J.publ. Hlth. 43*:665-76, 1953.
49. Emmons, C. W. Isolation of Histoplasma capsulatum from soil, *Publ. Hlth. Rep. 64*:892-96, 1949.
50. Emmons, C. W. Histoplasmosis: animal reservoirs and other sources in nature

of the pathogenic fungus, Histoplasma, *Amer. J. publ. Hlth. 40*:436-40, 1950.

51. Ajello, L. and Zeidberg, L. D. Isolation of Histoplasma capsulatum and Allescheria boydii from soil, *Science 113:* 662-63, 1951.
52. Zeidberg, L. D., Ajello, L., Dillon, A. and Runyon, L. C. Isolation of Histoplasma capsulatum from soil, *Amer. J. publ. Hlth. 42*:930-35, 1952.
53. Ajello, L. and Runyon, L. C. Infection of mice with single spores of Histoplasma capsulatum, *J. Bact. 66*:34-40, 1953.
54. Rowley, D. A. and Huber, M. Pathogenesis of experimental histoplasmosis in mice; measurement of infecting dosages of the yeast phase of Histoplasma capsulatum, *J. infect. Dis. 96:* 174-83, 1955.
55. Emmons, C. W. et al. Histoplasmosis, proved occurrence of inapparent infection in dogs, cats and other animals, *Amer. J. Hyg. 61*:40-44, 1955.
56. Rowley, D. A., Haberman, R. T. and Emmons, C. W. Histoplasmosis. pathologic studies of fifty cats and fifty dogs from Loudoun County, Virginia, *J. infect. Dis. 95*:98-108, 1954
57. Emmons, C. W. and Rowley, D. A. Isolation of Histoplasma capsulatum from fresh and deep-frozen peribronchial lymph nodes of naturally infected dogs by mouse inoculation, *J. Lab. clin. Med. 45*:303-07, 1955.

CURRENT CONCEPTS IN THE USE OF ANTIBIOTICS

*Transcription of a Panel Meeting on Therapeutics**

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* Presented in the Monthly Panel Meeting, Second Series, at The New York Academy of Medicine.

MODERATOR KNEELAND: It is a pleasure to welcome you here to the Monthly Panel Meeting on Therapeutics for the General Practitioner. The brochure which you all have in hand gives the panel members; however, I shall briefly introduce us. I am the Moderator, and I am in that happy position of having a panel of such bona fide experts that I shall not be required to say anything myself. At the extreme left is Dr. Alvan L. Barach, of Columbia University, the College of Physicians and Surgeons, whose work, I am sure, is familiar to all; Dr. David Habif is sitting second from the right; Dr. Habif, oddly enough, is a surgeon, and for several years now has been in charge of many of the antibiotic studies in surgical infections at the Presbyterian Hospital; Dr. Walsh McDermott is seated between Dr. Habif and Dr. Barach; it may surprise you as you look over this program to realize that a relative outsider is on the platform, but Dr. McDermott is not really an outsider, because he is a graduate of the College of Physicians and Surgeons, now temporarily residing at our sister institution on the East River; and Dr. Harry M. Rose, next to me, is Professor of Microbiology at the College of Physicians and Surgeons.

I am sure many questions will occur to you, and we shall be delighted if you would jot those down and give them to the usher. Meanwhile I should like each of these gentlemen to say a few well chosen words, and I shall start with Dr. Harry Rose, who is going to give us some of his mature reflections on antibiotics as they appeal to the microbiologist.

DR. HARRY M. ROSE: Although there have been remarkable advances in all branches of medical science during the past two decades there is probably no area in which progress has been so rapid or far-reaching as in the field of infectious diseases. The introduction of many effective chemotherapeutic agents or antibiotics and the general improvement of diagnostic laboratory procedures have provided means whereby the majority of the common bacterial infections may be cured or controlled. This is indeed so true today that the feeling unfortunately has become rather widespread in certain quarters that infectious diseases actually no longer present a significant problem. In consequence there is a certain lack of interest among practitioners, and this has bred, to some degree at least, an ignorance of the proper use of antibiotic drugs and of diagnostic procedures. As one example, I think we can cite the indiscriminate use of antibiotics, which unfortunately is rather widely

practiced at the present time. Actually, in spite of all the great advances which have been made it is of the utmost importance to the practicing physician that he know a good deal about the nature and the range of action of the different antibiotics which are commonly employed in clinical practice. He must know something about the characteristics of their effects on bacterial agents. He must be familiar with their toxic potentialities. He must understand the most effective ways of using them either singly or in combination. Last, but not least, he must know when not to use antibiotics as well as when to use them.

Before we get on farther into the more clinical part of this discussion by the other members of the panel, I would like to enter a plea for more adequate bacteriologic diagnosis in cases of apparent infectious disease. All too frequently the physician fails to obtain adequate or proper specimens before he initiates therapy with one or more antibiotic drugs. This, in my opinion, is most unwise and most unfortunate. If he does not have an adequate bacteriologic diagnosis he is hard put in many instances to select the best drugs which are to be used in the management of the individual patient. In addition, in certain instances he may find that sensitivity tests are subsequently required, and if the etiologic agent or agents have not been isolated beforehand such tests can not be carried out.

Going back to the list of items I referred to a moment ago, I might say from personal experience that it is astonishing how little physicians know in general about the spectrum of activity of the commonly used antibacterial agents. Some think, for example, that penicillin has a wide range of effect, whereas its clinical activity is entirely confined to the infections caused by gram-positive microorganisms. Some are totally unfamiliar with the range of activity of the less commonly used antibacterial agents such as neomycin or polymixin-B. Many are unfamiliar with cross-resistance to antibiotics, and in ignorance, they pursue therapy with an agent which is valueless because cross-resistance to it has developed through the prior administration of another drug. An example of this would be the administration of Terramycin to an individual whose microorganism had become resistant to Aureomycin.

The physician should understand the difference between a bacteriostatic and a bactericidal agent. Some of the commonly used antibiotics are solely bacteriostatic as used clinically whereas others are bactericidal. These effects are usually demonstrated by sensitivity tests,

as illustrated in the first slide.

(Slide) Here you will observe a plate on which a bacterium has been cultured and two discs containing antibiotics have been placed. There is a wide zone of inhibition of bacterial growth surrounding each disc. This is the so-called disc plate method of testing bacterial sensitivity to antibiotics and is the most widely used test in diagnostic laboratories. Tests of this sort give us some idea what the sensitivity of any given bacterium may be to the effect of any given antibiotic, but I should like to emphasize that the results are crude at best and frequently are unreliable. Many factors enter into this. We don't have time to go into them this afternoon, but among them I can mention the type of media which is employed and the size of the inoculum.

In many cases the disc plate sensitivity test is supplemented by the so-called tube dilution test, as shown in the next slide. (Slide) Here is a series of tubes containing different amounts of antibiotic ranging in concentration from 0.5 to 5 micrograms per milliliter, and you will observe that there is a cutoff point with respect to turbidity in the tubes. The end point dilution is taken as that which contains the smallest amount of antibiotic which prevents the appearance of visible turbidity, and this is usually read as the sensitivity level. In this particular instance it is 2.5 micrograms per milliliter. This, however, merely indicates how much of an antibiotic in a given medium under given conditions over a given period of time will prevent the multiplication of the bacteria to the point of visible turbidity. It is, in other words, a bacteriostatic test. It does not indicate whether the organism actually has been killed at this particular concentration or not.

A further test may be done as shown in the next slide where we see a comparison between the bacteriostatic and bactericidal end points. The sensitivity of a strain of Streptococcus fecalis is being examined. In the top row of tubes there is a series of dilutions of penicillin ranging from .02 to 30 units per milliliter. Visible growth is observed in the tubes up to and including 0.1 unit of penicillin per milliliter, but no visible growth is seen thereafter. The sensitivity level would therefore be reported as 0.2 units penicillin per milliliter. However, when subcultures were made from all these tubes into fresh media, it was found organisms were present in all the original tubes up to and including 10 units of penicillin per milliliter, and the first tube in which there was a bactericidal effect was that which contained 15 units of penicillin per

milliliter. There is, obviously, a wide difference between the bacteriostatic and the bactericidal end points. If the bacteriostatic end point were taken as the level at which the organism might be inhibited when treating the patient, one might conclude that relatively small doses of penicillin would be sufficient for therapy. In actual point of fact much more penicillin probably would be required. There are several types of infection in which it is important for us to know bactericidal end points in order to calculate therapy. The outstanding one, of course, is subacute bacterial endocarditis. Another example is certain infections of the urinary tract. In both bacterial endocarditis and infections of the urinary tract the defensive mechanisms of the host are not being brought to bear properly upon the infection. Bacteriostasis is not sufficient for cure. One must choose an antibacterial agent or combination of agents which will kill the organism rather than merely suppress its multiplication.

It goes without saying, of course, that physicians must be fully aware of the toxic potentialities of the various chemotherapeutic agents, and it is not my place to comment further on this point.

The physician should also know when it is appropriate to use antibiotics singly or in combination. In connection with the combined use of antibiotics there has been a good deal of comment concerning the synergistic action of antibiotics on the one hand and their antagonistic action on the other. That synergism may occur and be made use of clinically, there is no question. Antagonism, in my opinion at least, is another matter. It is true that antagonistic effects of antibiotics can be shown experimentally under carefully defined conditions, but it is doubtful whether antibiotic antagonism occurs very often at the clinical level.

Lastly, I should like to mention the fact that it is just as important for the clinician to know when not to use antibiotics as when to use them.

MODERATOR KNEELAND: I am a fully licensed physician, and occasionally I practice a little medicine. Dr. Rose has suggested that I don't use these agents very well. For that reason we have imported Dr. Walsh McDermott, who is one of the foremost students in the field of infectious diseases in this country, and I should like to have him illustrate what some of his views are in regard to antibiotics in internal medical diseases.

DR. WALSH MCDERMOTT: Dr. Kneeland, from my long acquaintanceship and friendship with Dr. Rose, it is only natural that I would know that I would be in no serious disagreement with him; nevertheless I do take issue with him on one point, and have a slight difference in emphasis perhaps on another point. The point on which I take issue is his statement about the improvements in diagnostic methods which we have seen in recent years. I quite agree with him that there have been very many improvements, but I would like to point out that almost without exception these improvements have to do with retrospective bacteriologic diagnosis, and we have seen no improvements in what we most desire, namely, diagnostic methods which are available to the clinician in proper time to be of real value.

Let me particularize on this. We are in a situation which occurs not infrequently in technologic development, where our power far outstrips our knowledge as to how to apply that power. We have the power in the form of these drugs, and we know that if the drugs are to be of maximum benefit they should be used when the patient is sick and not five or six days later. We also know that there are so many drugs that unless we know the identity of the infection in question we cannot make an intelligent choice of drug, yet we have no way of establishing that identity of infection for perhaps twenty-four hours or forty-eight hours, and in some instances four, five or six days thereafter. What are we going to do in such a situation? It seems to me that the only thing we, as physicians, can do is to become more perceptive clinicians and to learn how to draw shrewd microbiologic inferences from clinical phenomena, and use those inferences (at the same time taking the specimens for tests, as Dr. Rose pointed out) at the clinical level to give us help in that most important of all choices, namely, what drug or drugs shall be used in the treatment of that patient now, and not four or five days later when one has the culture.

The other point on which I take some issue with Dr. Rose has only to do with the question of emphasis, and I am pretty sure we have no fundamental disagreement here. We were discussing this matter before the panel meeting started. I realize that I may be guilty of making outrageous statements, but I told him only semi-facetiously that I thought if the doctors of America would stop being drug-sensitivity-test-happy, and pay very little attention to such things, that we would all be better off. I am particularly glad that he has taken so much trouble

to point out how one can become confused by these sensitivity tests, indeed to the point where there are really very few situations in which it makes sense to use them. The difference in emphasis has to do with the terms "bactericidal" and "bacteriostatic." As Dr. Rose pointed out, these are phenomena which apply to certain carefully specified in vitro conditions. They do not necessarily apply to situations which obtain in the body, and I think great harm has been done in all our thinking by too much preoccupation with the notion of whether a particular drug eradicates infection or merely supresses it. In actual fact, with relatively few exceptions, as all of us know, it is a very difficult thing to drive an infection out of the body.

I think I can sum up, Mr. Chairman, by saying that I believe we should face up to the fact that we don't have proper diagnostic methods to be used in proper time, and that our only recourse until such methods are available is to become better clinicians, and choose wisely and shrewdly on the basis of clinical phenomena.

MODERATOR KNEELAND: The internist approaches the problem of antibiotic therapy thinking mainly in terms of therapeusis either in acute overpowering or chronic disorders. Our surgical confreres have a different point of view in certain respects, and they are concerned to a much greater degree, I think, than we in medicine with the preventive or prophylactic use of antibiotics. In consequence, I have found that there is a slight divergence of view, say, between the eighth floor of Presbyterian Hospital and the twelfth floor, which cannot be accounted for on the basis of mountain sickness on the part of the surgeon. I would like Dr. Habif to comment on the use of antibiotics in surgery.

DR. DAVID HABIF: There is no question about the fact that antibiotics have changed the field of surgery considerably in that they made major surgery safer with a minimum of complications of infection. It is also clear that antibiotics are adjuvants of good surgery. They have prevented the formation of pus in many cases of cellulitis.

Antibiotics are primarily for the treatment of cellulitis whether the cellulitis is in the form of lymphangitis, pneumonitis, or osteomyelitis. On the other hand, the proper treatment for a collection of pus of moderate or large size is surgical drainage—with few exceptions, such as joint fluid collections and empyemas. These may be treated by repeated aspiration and instillation of antibiotics as well as giving systemic antibiotics. At times, surgical drainage may be indicated for these as

well. Reports in the literature concerning the successful treatment of large collections of purulent material with systemic antibiotics alone are exceptions. The treatment of established infection with a localized collection of pus is drainage.

As a corollary to this, surgeons appreciate a point which some practitioners are apt to forget. Pus tends to form within a period of three to five days. We have all observed the fact that antibiotics will control or remove cellulitis in the presence of pus so that the collection of pus is masked. The otolaryngologist encountered this with the mastoid problem. Beware of deep seated infections, as for example in the breast, which do not respond promptly within five days to antibiotic therapy. There may well be a collection of pus requiring surgical drainage.

Antibiotics are often employed to prevent infection following surgery particularly where mucous membrane-lined organs are cut across as in the lung, esophagus and remainder of the gastrointestinal tract. Here there is endogenous contamination as well as exogenous from the skin, air and possibly, upper respiratory tract of personnel in the operating room. Bones and joints do not have much power to prevent infection developing where there has been heavy contamination. Antibiotics used prophylactically as adjuvants of good surgery aid in a successful outcome without infection. The period of use prophylactically should be three to five days. The appearance of fever or its persistence where no other cause is apparent usually implies a collection of pus which is often masked because cellulitis has been abolished by antibiotics. Cancelling the antibiotic and allowing the cellulitis to return so that the collection of pus becomes clinically apparent is often more rewarding than increasing the dose, adding another, or replacing the drug. Most collections of pus are on top of the deep fascia and surgical drainage leads to a prompt recovery.

Let us consider the choice of antibiotics in surgery. Most surgical infections are due to gram-positive organisms,—predominantly, hemolytic Staphylococcus aureus and the streptococci. There is a growing number of infections due to the gram-negative organisms of the coli-aerogenes group. Penicillin is the best agent for hemolytic streptococcus, since one does not encounter resistance. The solution of the problem is not so easy with staphylococcus. Balbina Johnson found that 20 per cent of the staphylococci recovered from infections seen in the minor surgery clinic at the Presbyterian Hospital are resistant to the average

dose of penicillin, whereas 40 per cent of those recovered from in-hospital infections are resistant. This is most probably due to removal of the sensitive strains of these bacteria so that many of those remaining in the air and in the upper respiratory tract are of a resistant type. Exposure of a bacteriological plate for two hours in a surgical ward followed by incubation and sensitivity testing of the staphylococci reveals that better than 90 per cent are resistant.

Because of the finding of gram-negative organisms in many surgical infections, the combination of procaine penicillin and streptomycin is used. Streptomycin is a good drug and has a synergistic effect with penicillin. Unhappily, approximately 25 per cent of both gram-positive and gram-negative organisms develop some resistance to streptomycin within a period of five to seven days. We have given 300,000 units of procaine penicillin and 0.5 gm. of streptomycin every twelve hours.

As an alternative, or as a primary choice, the so-called broad-spectrum antibiotics namely, oxytetracycline (Terramycin), chlortetracycline (Aureomycin) and chloramphenicol (Chloromycetin) may be used. More recently, tetracycline has been made available and sold under the trade names of Achromycin and Tetracyn. The point has often been belabored that these agents are bacteriostatic and while this is true, they are nevertheless highly effective. Both bacteriocidal and bacteriostatic antibiotics are dependent upon host resistance, antibody reaction and the white blood corpuscles. It is interesting that the dose of broad-spectrum antibiotics employed today is defined more by that amount tolerated by patients in general without undue toxicity rather than correlation with sensitivity testing and blood levels obtained. Indeed, this correlation is often poor and one finds that a lower blood level in the serum than needed in the test tube to inhibit bacterial growth will often result in cure. As an example, a patient at Presbyterian Hospital with an E. coli septicemia secondary to a kidney infection was cured with Terramycin when the serum level achieved was 1 microgram per milliliter while 4 micrograms per milliliter were needed in vitro.

In 1952, we began using small doses of Terramycin both for prophylactic and therapeutic use. At that time the average dose in general use was 2 grams per 24 hours. We arrived at a dose of 250 milligrams every 12 hours and have continued with this schedule since then. The toxicity with this dosage has been 7 per cent. The serum levels vary between 0.6 and 1.2 micrograms per milliliter. We have had considerable experi-

ence as well with the intramuscular preparation of Terramycin using 100 gm. every 12 hours. The toxicity has been 3 per cent. A similar dosage schedule was followed with Aureomycin, but 1 gram per 24 hours was used for Chloromycetin because of its slightly more rapid excretion. We have used tetracycline in a dose of 250 milligrams every 12 hours by mouth with gratifying results. An intramuscular preparation of tetracycline has not been made available as yet.

In the treatment of cellulitis antibiotics may be selected for convenience by the physician engaged in outpatient practice. The importance of identification of the organism and its sensitivity has been emphasized and should be stressed. However, where culture may not be obtained and therapy is empirical and where pus has not formed as yet, a clinical response may be expected in 24 to 72 hours. This implies that the organism is sensitive to the antibiotic which is making contact. If this favorable response is not forthcoming, it is wiser to change to another agent rather than increase the dose. The possibility of a purulent collection should always be kept in mind and looked for. I must take some issue with Dr. Rose as regards the disc method of testing sensitivity. We believe this gives us a reasonably reliable guide as the expected response to an average dose of the antibiotic employed.

As to the other antibiotics, we have used neomycin orally for sterilizing the gastrointestinal tract, in some instances with bacitracin. It is an excellent drug for use locally in a 1 per cent concentration, but its toxicity prevents its parenteral administration. We have used polymyxin-B sulfate, both parenterally and locally for infections caused by gram-negative organisms; most notably Bacillus pyocyaneus. Its neuro- and nephro-toxicity resulting from parenteral use is tolerable and readily controllable. Erythromycin has also been used considerably for infections caused by hemolytic Staphylococcus aureus particularly where resistance to penicillin is demonstrated. Bacitracin is an excellent drug for both systemic and local use. Nephro-toxicity resulting from parenteral use is readily managed as indicated in many of the writings of Dr. Frank L. Meleney. It is the agent most frequently used at our hospital for local infections, often in combination with neomycin.

In closing may I say there is no antibiotic which does not have some toxicity. Further, there is no antibiotic to which some bacterial organisms are not resistant within a group which is known to be sensitive. In those instances where cultures are not obtainable, good clinical judg-

ment in observing the response of infection to an antibiotic is mandatory.

MODERATOR KNEELAND: Thank you, Dr. Habif.

Dr. Barach is, as you all know, a man of unlimited energy and ingenuity, having devised machinery which permits people to breathe or to stop breathing, if they prefer to stop breathing. He was one of the great pioneers of oxygen therapy and the absolute inventor of helium for uses other than levitation. His latest contribution is a machine which makes you cough,—the exsufflator which empties your entire bronchial tree. As the result of these interests he has found hanging around his neck a special clinic for patients with chronic intractable pulmonary conditions with which he endeavors to cope. For a number of years, since the introduction of antibiotics, he has accumulated a large experience in the management of chronic pulmonary disease, and has had a really enviable opportunity to observe some of the unfortunate side effects of these agents. I think, perhaps, he might have a few words to say on this subject.

DR. BARACH: Dr. Kneeland, I have been pushed into the field of antibiotic therapy, as you indicated, because many patients with bronchial asthma, emphysema, bronchiectasis and the more chronic infections of the bronchi known as chronic bronchitis without bronchiectatic change, have had pus in their sputum and since I have, reluctantly perhaps, come to some conclusions that don't entirely agree with those of the three speakers who have already presented their wisdom in this field, I feel somewhat out on a limb. Perhaps I might take a minute to remind you of the story of the inebriated gentleman who was walking with a friend and stepped accidentally into an elevator shaft; on his way down he called up and said, "Watch that first step, It's a lulu!" I feel I might be taking a similar step in the presence of these expert bacteriologists. Nevertheless, Dr. Kneeland has given me the opportunity to present our experiences in the treatment of chronic bronchopulmonary disease.

In those cases in which an acute respiratory infection takes place, in an individual not formerly ridden with a suppurative bronchitis, the treatment is generally not too difficult. Dr. McDermott said clinical judgment perhaps might reveal that a broad-spectrum antibiotic like tetracycline administered in a dosage of one gram or more a day for four or five days may result in the clearing of the infection. In order to avoid penicillin allergy, that would appear to be a good way to start.

Our main problems arise in attempts to arrest suppurative bronchial disease in patients with *chronic* pulmonary illness. The problem is especially complicated because almost all of them have an inpairment of drainage. An individual may cough up a certain amount of mucopurulent sputum but the secretions retained within the respiratory bronchioles and smaller bronchi maintain the chronic suppurative disease, swelling of the mucous membrane and dyspnea. Although I suppose some of the most dramatic examples of improvement in shortness of breath have taken place after the use of antibiotics, with the increase in the power of these drugs has come increased hazards in their employment.

In a study begun in 1941 on the inhalation of penicillin, we observed a good many individuals who had had chronic bronchitis, bronchiectasis, pulmonary emphysema or pulmonary fibrosis in whom penicillin aerosol resulted in an improvement of dyspnea and decrease in the purulent quality of the sputum. We had no deaths as the result of penicillin administration. In a certain number of cases we observed a Friedländer bacillus infection as revealed not simply by sputum culture but by the sudden appearance of increased quantities of yellow pus in the sputum, an occurrence described also by Weinstein. In these individuals the use of broad-spectrum antibiotics, preferably combined with streptomycin for six days, resulted in all of our cases in the elimination of that particular organism.

Some of our patients in whom penicillin, either by mouth or by aerosol, had been used for four to seven years were brought into the hospital in an attempt to rid them entirely of all suppuration. Broad-spectrum antibiotics like Terramycin were employed intravenously and by mouth in large doses. After temporary, dramatic improvement, some of those patients were readmitted to the hospital two weeks afterwards with extreme dyspnea and died, within a period of two weeks, of a Proteus pneumonia or a Pseudomonas infection. These were all cases in which bronchial drainage was severely impaired.

We have been very much interested in Dr. Habif's notion that the pharmacology of Terramycin was not worked out carefully enough. Although we have not found that 250 mg. of Terramycin twice a day was adequate, we have found one gram in four divided doses was effective in most cases. Since using that dosage and with attention paid to the attempt to improve bronchial drainage, we have not had a death

from contaminating organisms. Last week we did observe a death in a patient with lung cancer, and a Pseudomonas pulmonary infection developed during broad-spectrum antibiotic therapy.

When our clinical judgment indicates that relief of dyspnea may be the result of decreasing the obstructive element—dyspnea, i.e. by getting rid of infection in the bronchial wall, we are confronted with the problem of how to accomplish this in the patient with chronic suppurative pulmonary disease. In our clinic we have abandoned the use of intramuscular penicillin because of the steadily increasing number of allergic deaths and because, for the treatment of penicillin sensitive organisms in the respiratory tract, a million units orally twice a day gives an adequate blood level, according to the studies of Bunn, Pulaski and ourselves,—provided the organism is penicillin sensitive. Since practically all gram-positive organisms except a resistant Staphylococcus aureus are penicillin sensitive, that program of oral administration of larger doses of penicillin would appear to be the best because it can be used over a long period of time with very few side effects.

When we see a case in which the sputum, originally pus-containing, has become mucoid and then later suddenly again becomes pus ridden, we are likely to find one of the gram-negative organisms. Under these circumstances a week of broad-spectrum antibiotic therapy may be useful in clearing this invasion. Following this, a return to penicillin treatment is generally indicated. We use the following method of testing organism sensitivity,—Dr. Rose has agreed to do this at the hospital and we use it in the office. We put a swab into a sample of sputum and smear a blood plate with it and then place the sensitivity discs on that sputum smear. The next day, if we find a large area of inhibition around a disc, we can say that the drug that was used, or that the various drugs that showed this inhibiting effect, may be clinically useful. It is certainly important to do that on the *first* sputum sample. If we find, for example, a staphylococcus has been suppressed but Klebsiella is growing lightly around the disc that has Aureomycin, we would probably conclude that the staphylococcus was the invading organism. That first sensitivity test is the most important test that one can do. After the patient has had antibiotic therapy, the subsequent sensitivity tests may be very misleading for the reason that one generally finds that effective treatment against gram-positive organisms results in growth of gram-negative flora. We have had a man on penicillin aerosol for ten years whose sputum

regularly reveals colon bacilli on cultures and smears. He has not had a demonstrable infection with colon bacilli. If we then should have been guided by a sensitivity test which showed that this colon bacillus was sensitive to Terramycin, Aureomycin and Chloromycetin, we might have stopped treatment with a relatively innocent drug and used one of the broad-spectrum antibiotics, which are especially useful for actual infection with gram-negative organisms, when the sputum suddenly becomes purulent. However, these more powerful agents should never be used when the sputum is mucoid just because the sensitivity test indicates that the colon bacillus isolated is not sensitive to penicillin.

Let us assume the indication for using a broad-spectrum antibiotic is present. I think the situation has been significantly changed by two developments. The first is that modest advance has been made by the introduction of tetracycline, introduced by Lederle under the name of Achromycin. The studies of a number of people, including Finland, indicate that patients are much less apt to have nausea or diarrhea from this drug, and that cross-resistance and cross-sensitivity are very similar to that of Aureomycin and Terramycin. It may well be that in the great majority of cases tetracycline, in adequate daily dosage of at least 1.5 gm., will be preferred to Terramycin, Aureomycin or Chloromycetin. The second development is an observation that Dr. Hardy of the Lederle Laboratories has brought to my attention. He has noted that diarrhea is not due to monilia but is caused by the irritant effect of the drug on the mucous membrane of the gastrointestinal tract. If the intestinal content of Aureomycin is above 1 mg. per cc. of fluid, it will irritate the gut and cause irritant diarrhea. Later, as ulcerations appear, monilia infections and proctitis in males may occur. Our experience indicates that if a patient takes a full glass of milk,—and there is reason to believe that acidophilus milk containing lactobacilli is preferable,—with each 250 mg. or 500 mg. of drug, diarrhea is much less likely to occur. One would then have the opportunity of giving a drug like tetracycline for a four week period, first 250 mg. six times a day and then after the purulent quality of the sputum became less, three times a day.* Even with this modest yet definite improvement in the use of broad-spectrum antibiotics, our problems are not solved. We have had

* With regard to nausea effects, it is useless to compare tetracycline with Terramycin or Aureomycin unless adequate fluids, especially milk, are ingested at the same time.

pseudomonas infections, some of which could not be adequately controlled with polymyxin-B. In some of the patients in whom we have used the exsufflator that Dr. Kneeland was kind enough to mention, a half pint of mucopurulent secretion has been mechanically removed *after* the patient had eliminated as much as he could by his own voluntary cough. It is a very difficult problem to sterilize that amount of infected secretion, the secretion being moved back and forth along the bronchial tree. As many of you know, in cases with impaired pulmonary elasticity and retarded air flow, as in pulmonary emphysema, a vigorous cough will collapse the bronchi and prevent the mucus from coming out. In these cases an effective cough would be characterized by a deep inspiration and *moderately* vigorous cough but not a forceful cough. That type of cough will only deliver mucus from the tracheobronchial tree or bifurcation of the trachea upward into the mouth. The mucus in the smaller bronchi is apt to stay there for long periods, as shown by the character of the plugs, unless one uses some other method.

Many have had the experience of having patients die as the result of attempting to sterilize the bronchial tree of known pathogens only to have strains of bacteria, that formerly were rarely or never pathogenic, emerge and become invasive. It emphasizes what Dr. Habif has said about drainage. In the treatment of chronic bronchial infection every effort should be made to increase bronchial drainage; to have the patient, when necessary, sleep with the chest tilted head down at an angle so that gravity will be of help in effecting postural drainage. The lower lobes of the lungs will then be ventilated more effectively by diaphragmatic breathing. Exsufflation with negative pressure consists merely of a full inspiration followed by exposure of the bronchial tree to a negative pressure blower that provides an air wave of high velocity blowing past the mouth or nose, in such a way as to blow the secretions to the upper respiratory tract. You can realize the variety of illnesses in which impaired elimination of bronchial secretion occurs and how difficult is the treatment with antibiotics in chronic illness.

We have stressed the value of diaphragmatic breathing in patients with pulmonary disease. In many of the people in this audience costal breathing may be employed as the result of early training in schools. But the use of the diaphragm is necessary to aerate areas of the lung where bronchial secretions stagnate, namely, the bases of the lungs. An

increased movement of air from the lungs takes place by compressing the lower thorax and upper abdomen in such a way as to increase ventilation of the lungs in patients with pulmonary emphysema and bronchial asthma. Frequently, after inhaling a bronchodilator aerosol, which is one of the methods of opening the bronchi when in spasm, and compressing the chest and lower abdomen ten times during the expiratory cycle, the patient may be able to cough up mucus that was hitherto in the depths of the lungs.

(Slide) This simply is a picture of the result of exsufflation, sudden deflation of the lungs, resulting in air velocities leaving the mouth at two to five times faster rate than patients with chronic pulmonary suppuration can themselves produce.

The G. B. Spencer type of abdominal belt with two springs in it also aids the movement of the lower lobes of the lungs which is the site, in most instances, where suppurative disease is most apt to occur.

In answer to a question which has been submitted regarding the diarrhea which occurs as the result of antibiotic therapy, I would say that when diarrhea does take place as an irritant effect of the broad-spectrum antibiotics on the mucous membrane of the intestine, one should stop the drugs, particularly those that inhibit growth of the colon bacillus, until the diarrhea has been controlled. I think every effort should be made to control it as quickly as possible. I have seen it last as long as five months in people in whom vigorous measures have not been used. It may clear up spontaneously but I think that paregoric, Kaopectate, acidophilus milk and Yogurt might well be used. As to whether or not administration of acidophilus organisms actually has a value, I don't know. I am inclined to believe it does. I think Dr. Habif believes this also, but it is a difficult thing to prove. We did see one man with advanced bronchiectasis die of monilial peritonitis after ten days of vigorous Terramycin therapy,—he had developed ulcers in the large intestine and then monilial peritonitis occurred secondarily as the result of the ousting of the other organisms. They don't cause the diarrhea but they may become invasive on an irritated mucous membrane.

I want to say just two things more. In my opinion penicillin by mouth is the most valuable of the drugs that are the most feasible for long continued therapy. I want to say that in the case of respiratory infection with resistant Staphylococcus aureus, which may be resistant to five or ten units of penicillin per cc., and in which resistance to the

broad-spectrum antibiotics like Terramycin and Aureomycin is also present, the most effective way of eliminating the organism is by inhalation of penicillin by aerosol. By this means the concentration of penicillin in the sputum may be raised as high as fifty units or more per cc. of sputum. However, in some instances bronchospasm is provoked. Aerosol penicillin therapy for resistant staphylococcus infections may perhaps best be used in the following way: One million units of crystalline penicillin, dissolved in a mixture of 1 cc. propylene glycol, 0.5 to 1.0 cc. of 2.25 per cent racemic epinephrine and 12 cc. normal saline. Four cc. of this aerosol mixture is administered four times daily. With other non-resistant organisms this dosage, twice daily, is often the most feasible and practical way to control bronchial infection, especially bronchiectasis.

My second thought is that the Staphylococcus aureus actually represents the most important problem in chronic pulmonary disease. Chloromycetin is used in our clinic because in many instances sensitivity studies show that staphylococci may be most sensitive to Chloromycetin, and with a week's use the resistant organisms may disappear, and penicillin may again be employed.

We have seen some cases of pneumococcus infection. One case had a Pneumococcus XIX with bronchial infection for a period of many years previous. A course of antimicrobial therapy resulted in arrest of what was a chronic long-continued infection, with no recurrence during an observation period of two years. We have also seen patients in whom, with the use of penicillin, the improvement appeared to be linked with the disappearance of the non-hemolytic streptococcus organism.

Erythromycin and Magnamycin in chronic bronchopulmonary infections have been quite disappointing, although at times helpful but in the case of resistant staphylococcus not generally useful for longer than a week. One may then have to turn to a series of antibiotics such as Chloromycetin, or streptomycin with penicillin, or as I said, tetracycline in a dosage of 1.5 to 2.0 gm. if the organism is sensitive. Failing that, if the staphylococcus is still resistant, then at least in bronchopulmonary infections, the patient may need to give a week or ten days of his time and inhale penicillin by aerosol.

MODERATOR KNEELAND: A number of questions have come up. Obviously a number of people have been picking on Dr. Rose. Perhaps he would like to do a little rebutting and answer the questions that have

been directed towards the microbiological aspect of the problem.

DR. ROSE: I have four questions, Dr. Kneeland, all of which deal essentially with the same subject, so perhaps I can answer them together. The subject concerns antibiotic synergism and antagonism. As I indicated before, when antibiotics are administered in combination, synergistic effects may be observed with certain combinations and antagonistic effects with others. However, I should like to emphasize that the antagonism between antibiotics which has been demonstrated both in vitro and in vivo, has been so demonstrated under rigidly controlled experimental conditions, under which the levels of the antibiotics varied within fairly narrow limits. When those limits were exceeded the antagonism could no longer be demonstrated. This contrasts with synergism which occurs over a much wider range of antibiotic concentrations. There is reason to believe from experimental evidence, as well as from clinical observation, that antagonism between antibiotics is of little or no consequence in the management of human infections. It is possible, of course, that antagonism may exist occasionally but probably this is a rare phenomenon. On the other hand, synergism can be demonstrated quite regularly and is taken advantage of every day of the week in thousands of instances in the administration of antibiotic combinations. We know very little about the mode of action of these antibacterial agents. We do not understand the mechanisms of antibiotic synergism and antagonism. Perhaps in the future these problems will be elucidated but the answers are by no means apparent at the present time.

I have another question which asks which would be the antibiotic of choice in a urinary tract infection—cystitis—when penicillin, penicillin plus streptomycin and Gantrisin were of no value. It is difficult for me to answer this question because I don't know what caused the infection and I think it exemplifies what I said before about knowing the nature of the causative agent before being able to use antibiotics intelligently. In the case of a urinary tract infection, which apparently is resistant to antibiotic therapy, the best thing is to isolate the organism or organisms from the urine and to run a series of sensitivity tests to discover, if possible, which antibiotic or combination of antibiotics would seem to give the most hope of a cure and then to use that combination. If it does not work, try another. Eventually one may run out of combinations that will influence the infection, but the method that

I have indicated is the only rational one I know.

Dr. McDermott has remonstrated with me in a very mild and gentlemanly manner, as usual, for some remarks concerning sensitivity tests and diagnostic procedures and I must say that to a large extent I concur with his point of view. I still believe, however, that accurate diagnosis is the keystone of therapy and that if the physician does not know what he is dealing with he is like a pilot of a ship who is trying to navigate while blindfolded. There are many instances, to be sure, when the physician will have to rely on his experience and judgment in formulating a program of antibiotic therapy because he can find no way of making a specific bacteriologic or serologic diagnosis. Under those circumstances there is nothing to be done except to employ the antibiotic or combination of antibiotics which seem most logical and to observe whether there is or is not a beneficial response to therapy. Parenthetically, I might say that under such circumstances antibiotic therapy is often continued far too long a time. When antibiotics are administered and the patient does not seem to be responding, when the fever remains elevated and the signs and symptoms continue after a reasonable period of time, it is only logical to discontinue therapy, invoking the second law of therapeutics: If the treatment is not doing the patient any good, stop it.

MODERATOR KNEELAND: Thank you, Dr. Rose.

I cannot resist at this point putting in one little remark myself, which derives from something that Dr. Rose has indicated, and that is the deliberate use of antibiotics as a therapeutic trial in an endeavor to make a diagnosis. It seems to me there is one very important principle here, and that is that one should employ antibiotics in pyrexia of unknown origin in a well thought-out sequence, using the one first with the smallest range of antibacterial action and saving the antituberculosis agents until the last, because if one gets an effect in pyrexia of unknown origin, let us say with streptomycin, there is strong presumption that one may be dealing with tuberculosis, and that being established one is then committed to a long regimen of therapy. *Now Dr. Habif has a question or two, I believe.*

DR. HABIF: I have just one, Dr. Kneeland, and the question reads: What is the status of polymyxin-B? Is it felt that its toxicity should limit its use to severely ill patients? Polymyxin bisulfate is a good agent, which has its greatest usefulness in Pseudomonas aeruginosa infections. Its dosage is 2½ mg. per kg. of body weight in divided doses given every

eight hours. 2½ mg. per kilo is the twenty-four hour dosage. When given intramuscularly it is somewhat painful. Its greatest use is in septicemia and in urinary tract infections and also it is of value locally. As to its toxicity, it is neurotoxic and nephrotoxic. It is a long chain polypeptide like bacitracin, and, like bacitracin, if used properly, it may be considered a safe drug and its use need not be restricted only to the very ill patient.

MODERATOR KNEELAND: Dr. McDermott!

DR. MCDERMOTT: I have three questions here, Mr. Chairman. Two of them are on the same point, and one is a separate one. Both have to do with diagnosis, one about bacteriologic diagnosis with particular reference to the expense to the patient, and hence the interference with the clinician's freedom of action, and the other concerns the rationale of doing as so many people do,—i. e., start a patient on a broad-spectrum drug for a few days and switch to erythromycin or Magnamycin with the hope of avoiding the emergence of drug resistance. I think both of those are concerned with the same thing. Insofar as finances go, all diagnostic tests cost money, and we physicians have gradually found that we cannot get them all so we get the particular tests which we believe are worth the money. If they provide information to us of importance to the patient, then they are worth while, and I think in this case, namely, the treatment of a patient with infection, there is no question about the fact that such tests should be obtained. As Dr. Rose pointed out, he and I are in agreement; indeed what we are doing is presenting a three-plank program. He is emphasizing two of the planks and I have been emphasizing the middle plank. Our three-plank program is really, first, that it is of the greatest importance to obtain the specimens for an etiologic diagnosis in every case of an illness which might be an infection, although one must wait for a result until the microorganisms have synthesized enough protoplasm to make themselves seen, which is twenty-four or forty-eight hours, or three or four days. Second, it is likewise of importance to the clinician to start therapy, and start therapy shrewdly. Indeed, we should perhaps be learning more about diseases than we are about drugs at this stage when there are so many drugs. Plank three, which I am particularly glad he emphasized, is stop drug therapy if what you are doing does not make sense. It would be so much better, to draw an extreme case, to give five drugs on day one, if we could only be certain that we would narrow

it down to two, or one on days two or three, on the basis of the information obtained from the laboratory. Instead we make ourselves prisoners of our therapy and proceed to continue therapy with drugs which are no longer of value. Mr. Chairman, I might be accused of speaking in generalities, and if I could particularize I would take one condition.

MODERATOR KNEELAND: Indeed, you may.

DR. MCDERMOTT: Let us assume the physician is called to see a patient with a febrile illness which is in fact pneumonia. What can he do? He certainly can demonstrate that the patient has pneumonia. He does not need a laboratory for that. It is helpful if he can get a total leukocyte count, but we all regard that as one of the essentials in practice these days anyway, and it is not an inordinately expensive procedure. Given those facts he should then obtain material, namely, sputum, blood, and a nasopharyngeal swab for culture, and should proceed to analyze the situation. He has already established the patient has pneumonia; now the next decision he has to make is which drug or drugs is appropriate for this patient's pneumonia and not for all pneumonias. How should he go about that? The first question—and it has to be answered right then and there, not four days later—has to be answered on clinical grounds: Does this patient have a very severe pneumonia, or does this patient have only a moderately severe or mild pneumonia? Certainly that is a decision which all of us are perfectly equipped to make. What difference does it make? A great deal of difference. If the patient has an unusually severe pneumonia, it is our practice to administer streptomycin and penicillin right away for the first night. Why those particular drugs? What could be causing an unusually severe pneumonia? Well, the things which could be causing it are about four or five in number. To the more extremely ill pneumococcal patients, the penicillin would be valuable; in Friedländer's pneumonia, the streptomycin would be of value; in suppurative pneumonia, the condition which gives rise to lung abscess, the two together would be the proper therapy, also in staphylococcal pneumonia. What would be the proper therapy for beta hemolytic streptococci? Penicillin or Terramycin. On the following day, if a diagnosis of Friedländer's pneumonia is made, the culture having grown out (because that is one of the more rapidly growing organisms), one could stop the penicillin and add chloramphenicol, if you will, or one of the tetracyclines. Similarly, if pneumococci were recovered, stop the streptomycin and continue with

the penicillin. This is the manner in which one uses the material gathered before therapy to guide our treatment after the start of the therapy. The important thing is to make one's initial decision on the probabilities as to what this particular clinical syndrome might represent. If the patient has a mild or moderate pneumonia I see no reason then for not giving one of the tetracycline drugs, and no particular reason to choose one over the other. It is established that the tetracycline drugs are as good as penicillin in the treatment of pneumococcal pneumonia insofar as medical recovery is concerned. It has not been established that they are as good as penicillin in preventing pneumococcal meningitis or the other complications, although there is no reason why they are not. So Mr. Chairman, that is the example I would use as to what I mean and what Dr. Rose means by saying that it is important to establish the diagnosis from the laboratory standpoint, but while doing that it is more important to know more about what infections might be present and their clinical manifestations, and to choose drugs accordingly, than it ever was before. The day has long since passed when we can give all the available drugs in the form of one drug, namely, sulfonamide.

The other question was, would the other gentlemen comment on Dr. Barach's statements that tetracycline will replace the other broad-spectrum antibiotics? For myself all I can say is that I have no personal experience. The information which I have heard and read is exactly as outlined by Dr. Barach.

MODERATOR KNEELAND: I think this ends the question period and therefore we can assume this meeting is adjourned.

VENESECTION, BEFORE HARVEY AND AFTER*

DELAVAN V. HOLMAN

VENESECTION, or bloodletting, as it was commonly called, is one of the oldest human efforts at therapy. If one follows the course of a single procedure such as this down through history, it affords a review of the development of medicine and, in this instance, of civilization itself.

No one knows when or why bloodletting was adopted as a form of treatment and prophylaxis for human ills. Its beginnings are lost in antiquity and it was undoubtedly instituted on a purely empirical basis. It continued to be so used until quite recent times.

It is worth emphasizing here the difference between an empirical and a scientific remedy because therein lies the difference between the so-called art and science of medicine. We today like to think that the science of medicine is a modern development. However, each generation of medical men has made some effort to rationalize their art. This is true of venesection.

Before we review its history it has occurred to me that we might all benefit by consideration of its present status. Is venesection still used and, if so, for what conditions and under what circumstances? With how much success? Most important of all, what has our own generation learned about the action of venesection on the body?

We shall see that in past centuries there has been much emotionally colored controversy for and against bloodletting. It seems a fairly safe assumption, however, that no form of treatment could have been used as extensively over so many centuries without having some basic value.

I made a start by studying the current medical literature. The cumulative medical index listed eight English language articles during the last five years in which venesection was mentioned in the title. There were several others in foreign languages, chiefly German. Four of the English language articles gave a minimum of attention to clinical aspects of venesection, were primarily concerned with the technique for use in

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animal studies on iron metabolism and blood regeneration. This answers our first question fairly well and we know from our own attitudes and experiences, as well as those of our colleagues in the practice of medicine here in New York, that venesection is not a highly popular form of treatment.

All this is not to say that venesections are unknown to modern medicine. The contrary is true, but for a new purpose. Blood transfusion has become almost as popular as venesection used to be and for each transfusion, some donor must necessarily have had a venesection. One interesting aspect of the history of bloodletting is to realize the enormous amount of good blood that was wasted. How fortunate it would be if some part of our ancestors' faith in prophylactic bleeding could have survived to motivate modern blood donors.

Much of what we now know about the physiology of bloodletting has come from a study of blood donors. The volume of blood customarily removed for transfusion is similar to the volume for treatment. It has therefore been possible to follow and compare the effects in both healthy and diseased states.

When a pint of blood (500 cc.) is withdrawn in a healthy individual the organism is said[1] to replace it quantitatively within an hour or so. Qualitatively, however, there is a further delay. Fowler and Barer[2] studied two hundred healthy donors and observed an average fall of 2.3 grams per cent of hemoglobin after the removal of 550 cc. of blood. They followed regeneration and observed that hemoglobin was restored at a rate of between .040-.049 grams per cent per day. Men were somewhat more rapid than women. Erythrocytes did not regain their former concentration for approximately seven weeks, depending considerably upon the amount of available iron and high quality protein in the diet.

If blood loss is large (more than 10 per cent of the total blood volume) and sudden, systemic blood pressure falls.[3] This is a well known protective mechanism to aid blood clotting. If the volume of blood lost does not exceed 30 to 40 per cent of the total, systolic, diastolic and pulse pressures rise again after about thirty minutes as a result of various compensatory mechanisms. The heart rate increases, peripheral vasoconstriction empties non-vital areas of blood, and the rate and depth of respiration increase to act as a subsidiary circulatory pump. In the dog, the spleen contracts and empties quantities of erythrocytes into the blood stream; it is not certain, however, that this happens in man. Pro-

teins, as well as fluids, are drawn into the blood stream from the tissues.

If larger volumes (more than 30 to 40 per cent) are lost suddenly, the organism is usually unable to survive unless the loss is promptly replaced. Repeated smaller bleedings may produce a state of chronic anemia when the total amount removed is in excess of natural recuperative powers.

With these essential facts in mind, I next consulted recent editions of standard textbooks on internal medicine and therapeutics. I could find ten separate conditions where venesection was recommended for treatment in some stage of disease. These fall naturally into a very few groups when classified according to mechanism of action.

1. Venesection is still recommended in erythremia to rid the body of the excessive red cell elements. It is being supplanted, however, by radioactive phosphorus, which does the same thing better. Venesection is recommended for similar effect in some stages of hemochromatosis to rid the body of excess iron. Massive bleeding with simultaneous replacement has been developed for erythroblastosis; is occasionally recommended for leukemia and hemophilia.

2. Venesection can be used successfully for emergency relief in crises of pulmonary congestion and edema in left ventricular failure, and sometimes in acute nephritis, pneumonia, atropine poisoning and so-called blast syndrome. As we shall see, Hippocrates recognized this indication although he apparently did not know why it was beneficial. Most modern therapists reserve venesection for emergencies in plethoric persons pending institution of oxygen, digitalis and diuretics, which have a more enduring effect.

3. Bloodletting is still mentioned for control of arterial hypertension, especially in plethoric individuals who appear threatened with congestive heart failure or apoplexy. McMichael and his co-workers[4] report that venesection causes a prompt fall of right auricular pressure, cardiac output increases, peripheral resistance is depressed and systemic blood pressure falls. These same workers found a parallel effect from digitalis which persists longer.

Hypertensive patients not in circulatory failure have often been observed to get symptomatic relief from venesection for varying periods of time. Some observers have taken the view that this effect was purely psychological. Others, such as Edwards and Bordenave,[5] studied a group of blood donors with essential hypertension. They found an immediate

rise in systolic pressure for the first hour after bleeding, followed by an appreciable lowering of systolic and diastolic levels accompanied by relief of symptoms and an improved sense of well being in 95 per cent of their cases. This effect persisted on an average for eight weeks. If the early promise of Rauwolfia and similar recently introduced anti-hypertensive agents is fulfilled, this indication for venesection is apt to be supplanted also.

Thus it is clear, not only is venesection infrequently used nowadays but within our own immediate experience the few remaining indications are being supplanted by newer and better remedies.

With this in mind, let us go back and sketch the historical career of venesection.

The name comes from the Latin, *vena* for vein and *secare* meaning to cut. Antiquity recognized two techniques of bloodletting. Large amounts from a vein or artery were called "general bloodletting"; leeching, scarification or cupping were known as "local bloodletting."

Bloodletting,[6] however, considerably antedated Roman times. It was believed to have been practiced by prehistoric man. It has been suggested that witnessing the effects of accidental hemorrhage and observing the natural periodic process of menstruation may have directed medical minds to hygienic and prophylactic advantages of depletion. Emesis and purgation were usually closely allied measures.

The ancient Egyptians were said by Herodotus to have purged themselves three times in succession, once a month. They are known to have permitted circumcision and venesection operations despite their religious horror of mutilation of the human body. Lancets of stone and cups made from the pointed ends of cattle horns have been found in excellent preservation in ancient Egyptian sarcophagi.

Bartels and other writers on primitive medicine have reported that savages commonly used sharp thorns or roots, fishes' teeth and sharpened stones to open abscesses, remove cataracts and open veins.

The Jews probably learned the art of venesection from the Egyptians. It is not mentioned in the Bible but both venesection and cupping were evidently well known by the time the Talmud, the Hebrew Lawbook, was written around the Second Century, A.D. They probably used primitive, crude leaf-shaped flint knives sharpened to an edge or point. These instruments were held in great veneration by all ancient peoples. The Jews began to use venesection prophylactically.

They called it "dietetic" bloodletting and performed it once a month until the age of sixty and less often thereafter. "Full-blooded" persons were sometimes bled so energetically that they fainted or fell into convulsions. The rule was to remove one-sixth to one-eighth part of the total blood volume but the operation was anything but exact. Serious and fatal mistakes undoubtedly occurred. Yet there was evidence of such faith among lay people by this time that they attributed failures to the victim rather than the bad judgment of the operator.

Persians, Chaldeans and ancient Chinese apparently did not take up venesection although they must have been made familiar with its use by their neighbors through commerce and wars. It found great favor, however, with the Hindus who began to bleed healthy people, except Brahmans or princes, twice a year at the turn of the season. A lancet was used and Susutra, one of their ancient physicians, recommended bleeding directly from one of the veins of the external genitals for venereal infection. In some parts of Asia, especially Bengal, leeches were in common use from earliest times.

In the Classical Period, Hippocrates, born around 460 B. C., was the first to use venesection extensively. He and his school are generally credited with its introduction, both as a remedy and prophylactic measure. He wrote, "Bleed in the acute infections if the disease appears strong and the patients be in the vigor of life, and if they have strength." He also recommended bleeding for 1) engorged hypochondria in case the swelling is not meteorism, 2) orthopnea without expectoration when the impeded respiration is not caused by a discharge of pus into the pleural sac and subsequent pulmonary compression, but when it is due to air hunger, 3) violent pains in the regions of liver and spleen, and 4) inflammations and pains above the diaphragm.

Hippocrates developed a tourniquet bandage, used as now, tight enough to impede venous return without interrupting arterial flow. He advised that the wound of skin and vein be in apposition to each other, used a curved bistoury of medium width and had a carefully graded system to guide on the volume of bleeding. The season of the year, the age of the patient and his constitution and color of his blood were all taken into consideration. If the blood was thick and dark, the so-called buffy coat, bleeding was stopped as soon as it became red and clear; or if it was red to begin with, when it became darker. When he bled for severe pain, he kept at it until the patient fainted from cerebral anemia.

This seems heroic to us but it must be remembered he had no other anesthetics.

Hippocrates advocated so-called *revulsive* bleeding. The location of vein puncture seems rather ridiculous to us now with present knowledge of continuity of the circulation but was considered critically important in ancient and medieval times. *Revulsive* bleeding ruled that the individual should be bled from the same side of his body as the inflammation, pain or other symptoms being treated were located. As we shall see, another school of thought developed which held that it was better to bleed from the opposite side of the body. This was called *derivative* bleeding.

Asclepiades of Prusa is credited with establishing Greek medicine in Rome. He was opposed to drastic emesis, purgation and venesection. He did accept one indication for venesection, to relieve intractable pain. There were others following the Hippocratic period who opposed the use of venesection. Very possibly in the intervening generations, many abuses had appeared as indeed has been the experience down through the long centuries of its use.

Celsus and Galen revived and expanded the list of diseases to be treated. Celsus in particular urged training in the technique of venesection and pointed out that the ancient Hindus acquired skill by practicing extensively on the veins of plants before treating humans.

Aretaeus, the Cappadocian, left one of the best treatises on the practice of medicine in antiquity. He recommended bleeding for a long list of diseases, introduced a highly specialized technique. He recommended bleeding from the frontal vein of the forehead in headache, epilepsy and vertigo; from the tongue veins for throat affections; the nasal veins for hemoptysis and headache; scarification of the pubes or venesection at the ankle in hysteria. This is one of the first evidences of what came to be called "points of election" which became such a complicated feature in the venesection manikins and calendars published during the Middle Ages in Europe.

The Arabians became devout followers of Galen and enthusiastic bloodletters. They introduced so-called *derivative* bleeding mentioned above. They bled from the side of the body opposite to the lesion under treatment.

In the Twelfth Century, there was an important medical publication called the *Regimen Sanitas* (code of health). It was a long poem in

hexameter Latin verses written by unknown authors and for the benefit of King Robert of Normandy who was cured by bleeding of a wound at Salerno in 1101. The *Regimen* gives detailed instructions for personal hygiene and diet, with a special section on bloodletting, prophylactic as well as therapeutic. It was translated into every language and circularized throughout Europe. The superstition so characteristic of the Dark Ages was apparent in the beginning emphasis on astrology.

As time went on, superstition became increasingly dominant until by the Seventeenth Century medical diagnosis, as well as treatment, was arrived at by study of the conjunction of the planets. A physical examination would have only confused the issue and was therefore dispensed with. The sun, moon, planets and signs of the Zodiac were each assigned a special share in the control of the body. A single glance at their position told the physician the trouble. Once he had his diagnosis, he had only to consult his venesection manikin on which were shown fifty-three possible sites where a vein could be reached with a lancet. The diagnosis and treatment thus far were fairly simple. The part that took skill was to decide on the exact moment to strike. Great care was taken to be sure that conditions prevailing at that fateful hour were favorable to the patient and his disease. Numerology came to have an important part in determining favorable dates and belief in the good luck attendant upon being bled on certain dates became so deeply rooted that even into the Nineteenth Century they continued to be published on the calendar.

In the Middle Ages there were a few reliable physicians and surgeons. Although these condoned and prescribed venesection, they seldom did the operation. Instead, it fell into the hands of a motley group of "barbers, bathkeepers, sow-gelders and strolling incisors". The morals of the practitioners fell to a low ebb comparable only to their incompetence. While they literally drew rivers of blood, bitter arguments raged between their more learned medical sponsors on the relative merits of the *derivative* vs. *revulsive* bleeding. Even some of the Popes and crowned heads were drawn into the controversy and one famous Parisian physician was forced into exile because of it. The controversy was finally resolved in favor of Hippocratic revulsive bleeding by the fortuitous death of a close relative of Charles V, Emperor of Germany. This relative happened to have been bled by the *derivative* method and his death was obviously the result and the method at fault!

From the Fifteenth Century, we have contemporary pictures of healthy people being bled in the public baths. There we see nude men and women huddled together in a common bath vat or steamroom; some eating, drinking wine, playing musical instruments, reading books, soaking, perspiring while one individual is spouting blood from his median basilic vein.

The modern development of venesection came with the discovery of the circulation of blood by William Harvey (1578-1657). The change was not immediate. Gradually, independent thinkers like Sydenham began to apply reason and bring some order out of chaos. Yet some of the worst excesses continued to occur on into the Eighteenth Century, especially in France. The Hôtel-Dieu is said to have run red with blood. Sick patients were alternately purged and bled; ten and even twelve venesections were the rule, and sometimes twenty or thirty. It is recorded that one French physician named Patin bled a colleague thirty-two successive times for continued fever and had himself bled seven times for a simple cold in the head. One female patient suffering from convulsions in the Civic Hospital of Prague was said to have been bled in all eight hundred times. They bled for obstinate hemorrhages of penetrating wounds of the chest incurred by bullets and bayonets in battle. Some of these wounded patients had 300-500 cc. of blood withdrawn as many as six to ten times.

The use of venesection spread to the American Colonies. Benjamin Rush used it extensively; General Washington was said to have lost his life because of it.

Gradually, however, reason began to take effect. Louis and others took statistical record of their mortality treating acute infections, such as pneumonia and typhoid fever, with and without venesection. The findings were not flattering to venesection. Novelists, such as Charles Dickens and Reade, helped influence the popular mind but actually it was not until the time of Jenner and Gull (circa 1860) that venesection was officially discarded in the modern sense.

In 1895, Dyes reported saving the life of a young woman believed dying of chlorosis. This event stimulated renewed interest, reflected in publication of at least two comprehensive monographs on theory and practice.[6] Only within contemporary experience has venesection gone out of favor as the treatment of choice for toxemia, hypertension or any diseased state wherein local or general congestion was suspected.

From even this brief review of its history, it is clear that venesection has had a most spectacular and long career. Its period of maximum popularity paralleled eras of low cultural ebb when ignorance and superstition were at their worst. Despite this disreputable association, venesection cannot be dismissed lightly or its past use entirely condemned. Medicine, like art and religion, is truly a product of its own age. Even ethical medical practitioners, then as now, must satisfy their patients that "something is being done". Every physician knows that the most desperate chance may become acceptable in time of great human need.

There can be no question that human need was desperate and ancient physicians poorly equipped to meet it. It is difficult for us now to imagine medical practice without most of the modern remedies we take for granted. With this in mind we can readily understand the dramatic appeal of bloodletting. It was an operation calculated to take the patient's mind off his ills and convince him everything possible was being done to restore him to health.

In addition, as we have seen, venesection undoubtedly was a real help when used properly. There are acknowledged beneficial effects under some circumstances. However, with few exceptions, newer remedies have been developed which do a better job easily. The trend has continued well into contemporary experience.

It is always dangerous to try to foretell the future. The future of therapeutic venesection is no exception. It now seems probable, however, that one use is likely to survive. I refer to emergency relief for excessive venous pressure.

The fate of prophylactic venesection seems less certain. Currently, interest in it as a stress-stimulant is at a very low ebb despite the fact there is some evidence to show that the rate and quality of blood cells and plasma protein regeneration are improved by controlled bleeding. For centuries normal people were bled periodically to insure continued health. Further studies of the physiological effects could, if they confirm and extend understanding of the benefits, revive popular faith. This in turn would have an obvious propaganda value for prospective blood donors. In this way, with little extra effort, double benefit might accrue to both the healthy and the sick as prophylactic venesection came to supply ever increasing volumes of blood for transfusion.

(REFERENCES ON NEXT PAGE)

REFERENCES

1. Best, C. H. and Taylor, N. B. *The physiological basis for medical practice.* 5.ed. Baltimore, Williams & Wilkins Co., 1950, p. 26.
2. Fowler, W. M. and Barer, A. P. Rate of hemoglobin regeneration in blood donors, *J. Amer. med. Assoc. 118*:421-26, 1942.
3. Wiggers, C. J. *Physiology in health and disease.* 5 ed. Philadelphia, Lea & Febiger, 1949, p. 802.
4. Howarth, S., McMichael, J. and Sharpey-Schafer, E. P. Effects of venesection in low output heart failure, *Clin. Sci. 6*:41-50, 1946; and Effects of oxygen, venesection and digitalis in heart failure from diseases of the lungs, *ibid. 6*:187-96, 1947.
5. Edwards, J. W. and Bordenave, J. Effect of blood donations on blood pressure of hypertensives, *U. S. Nav. med. Bull. 46*:736-39, 1946.
6. Garrison, F. H. History of bloodletting, in Dutton, W. F. *Hand-Book of venesection*, Philadelphia, F. A. Davis Co., 1916, pp. 1-40.
   Stern, H. *Theory and practice of bloodletting*, New York, Rebman Co., 1915, pp. 3-32.

THE ANTECEDENTS OF BLOOD TRANSFER*

LESTER BLUM and WILLIAM M. NELSON, Ph.D.

THE association of blood with life itself is among the primitive concepts of man. In the picturesque phraseology of the Old Testament, blood is a synonym for vitality, emotion and heritage. It constitutes the basis of one of the plagues described in Exodus when Moses caused all the rivers and streams of Egypt to run red.[1] It is not surprising that both Pliny and Celsus describe the patricians rushing from their seats in the Coliseum down into the arena to drink the freshly flowing blood of dying gladiators.[2]

The thought that all these vital properties could be transmitted by the act of transfusion is of ancient origin. A rational approach to this end, however, necessarily awaited a clear understanding of the nature of the circulation. This was provided by William Harvey in his *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*, published at Frankfort in 1628.

Although animal and human blood had already been administered by infusion, the first successful transfusions in animals were evidently performed on dogs by Richard Lower at Oxford in 1665.[3] He connected the blood vessels with quills and silver tubes.

Just two years later, on June 15, 1667, the first recorded transfusion in man was accomplished by Jean Baptiste Denis at Paris. In a famous letter[4] written ten days thereafter, Denis stated that in his preliminary experimental work none of nineteen dogs died. He connected the crural artery of the donor animal to the jugular vein of the recipient. He was thus emboldened to transmit 9 ounces of blood from the carotid artery of a lamb to a sixteen-year old asthenic youth who had been repeatedly bled for fever.

Denis' second case was that of a forty-five year old man who was first bled 10 ounces and then given 20 ounces from the crural artery

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of a lamb. Immediately following the procedure, the patient killed and dressed the lamb and then went off to a tavern to drink part of the money "given him for the day's business". The conclusion is inescapable that this account establishes the priority of the first paid recipient long before paid donors appeared on the scene.

As a result of difficulties encountered in transfusing a third patient, Denis suffered for years because of litigation with an ungrateful widow. The procedure fell into disrepute and little was done in this field for another century and a half.

In 1821, Prevost and Dumas showed that exsanguinated animals could be revived by transfusion but not by serum or water solution.

Several years later, in 1828, James Blundell[5] reported his rediscovery of transfusion in the treatment of postpartum hemorrhage. In a classic article in the *Lancet* he described eleven transfusions performed despite failure in the first four attempts. Blundell used human donors and emphasized that the blood of an alien species was unsuitable. He warned about the necessity for careful observation of the recipient throughout the procedure. There is an illustration of his "Gravitator" which was a metal channel with an upper basin for collection of the standing donor's blood leading down to a silver tube placed in the basilic vein of the recumbent recipient. The passage was flushed with clean water or warm milk at intervals to wash out clots.

It should be noted that at this time there lived and worked the great Jean Leonard Marie Poiseuille (1799-1869) who is considered the father of rheology by the physicists who recognized his genius many years before his fellow physicians appreciated his contributions. The importance of Poiseuille's work in basic concepts of blood flow and circulatory dynamics is only being understood in our time.

A generation after Blundell, Franz Gesellius[6] developed an ingenious apparatus for the collection of capillary blood for transfusion. It is of purely historical interest.

Although Landois,[7] in 1874, demonstrated that the serum of one species agglutinated or dissolved the corpuscles of others, it is surprising to note that at the German Surgical Congress of that year, thirty-one transfusions with sheep's blood were reported.

In the last quarter of the Nineteenth Century, despite the great interest in this procedure and the arguments as to whether blood should be injected towards the heart or away from it, the large number of

Fig. 1—The Ancient Syringe Ritual of the Hindu. (From Ewbank, T.[17] *Hydraulic and other machines*. New York, Scribner, 1870. Reprinted by permission of the publisher.)

adverse reactions resulted in far more saline solution being used than blood. It was not until the dawn of the Twentieth Century that the most important step in the establishment of transfusion as a scientific procedure of the highest therapeutic importance was made. In 1901 Landsteiner[8] described the blood types and laid the foundation for this entire branch of hematology. His work explained the troublesome and unpredictable reactions of the past and laid the basis for the removal of most of the risk of transfusion. Several years were to pass before the practical application of his contribution by Ottenberg[9] became part of clinical technique.

Although direct transfusion by syringe was systematized by Lindeman[10] and Unger[11] by the time of the outbreak of World War I, the procedure did not always run off smoothly and required operating room conditions to insure successful handling. The chief problem remaining was that of controlling the physical state of blood so that it stayed fluid and lost little of its other properties.

In all probability, the first step in this direction was taken by Poiseuille,[12] in 1823 when he employed potassium bicarbonate solution to keep the tubing clear in his studies of blood pressure by direct manometry in millimeters of mercury. In the latter Nineteenth Century sodium phosphate and mechanical defibrination were used to retard clotting. In the same year as Landsteiner's publication, Bordet and Gengou[13] showed that clotting could be inhibited by physical means such as the paraffin coating of vessels and tubing. A significant step forward in the efficient handling of blood was the observation of Hustin[14] that sodium citrate and dextrose indefinitely retarded clotting and permitted the precise, unhurried, clean handling of blood which led to the indirect method of transfusion most common today. The first citrated transfusion, credited to Luis Agote,[15] was performed in Buenos Aires on November 14, 1914. At the same time Lewisohn[16] was solving the problem in New York.

Although heparin, the ideal and natural anticoagulant, was not to be generally available for another twenty-five years, it is a sad fact that all the requisites for the use of blood, as we know them today, were at hand shortly after World War I got under way. Blood banks were not established until thirty years later. In short, the real obstacle to progress was the remarkable lack of imagination shown by our profession in being unable to benefit immediately from the advances discovered in the laboratory.

This, then, is a bare outline of the major steps necessary to provide the large amounts of blood used in surgery today. The successful storage for days outside the body of this tissue in the fluid state, not only provided the ideal remedy for hemorrhage, shock and debilitating disease but also made possible the exploitation of other vital functions of blood such as those connected with oxygenation and the excretion of waste products.

The Conduction of Blood Outside Vascular Channels

In Lower's original experiments the blood vessels were connected with quills and silver tubes. Blundell,[5] recognizing the importance of pressure in the introduction of satisfactory quantities before clotting took place, employed his "Gravitator" which was a rather complex, elongated, silver tube for establishing a head of pressure equal to most of the height of the standing donor. This simple apparatus takes prece-

Fig. 2—The Roman Piston Bellows. (From Ewbank, T.[9] *Hydraulic and other machines.* New York, Scribner, 1870. Reprinted by permission of the publisher.)

dence over the syringe in the actual transfer of blood. In the latter Nineteenth Century syringes with stopcocks were employed.

The syringe is mentioned as an instrument in the embalming procedure of ancient Egypt. It was employed by the Hindus in religious rites that date back to antiquity.[17] It reached its highest development in transfusion in the apparatus of Unger.[11] Its use for the transfer of large amounts of blood over long periods of time is rather limited because the turbulence which is a necessary part of its rapid function results in a forbidding degree of hemolysis. In the latter Nineteenth Century there also appeared the milking type of pump for transfusion. This was latterly preferred by von Issekutz[18] and independently by DeBakey.[19] Movement of the blood column was obtained by alternate compression and relaxation of the tube through which the blood ran. This could be effected by rollers or by separate levers. It is considered satisfactory enough today to be the most common type of propellent used in extracorporeal shunting.

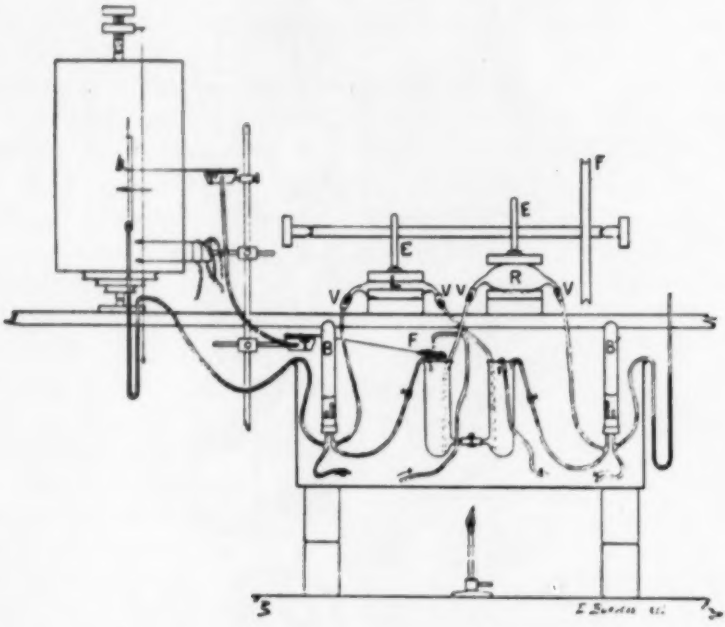

Fig. 3—The Blood Pump of Embley and Martin—1905. (From Embley, E. H. and Martin, C. J.[20] in *Journal of Physiology 32*:147-58, 1905. Reprinted by permission of the publisher, Cambridge University Press.)

Other types of rotary or reciprocating pumps have been used clinically and in the laboratory during the last fifty years. Some are direct modifications of pump types used in antiquity for irrigation such as the Chinese noria, the Persian sakias, the Roman piston bellows and the Egyptian tympanum. All of these are either rotary or reciprocating types.

The problem of propelling blood outside the body arose in the laboratory in the latter Nineteenth and early Twentieth Centuries when studies of the physiology of organs and tissues under partially controlled conditions became feasible. Although too much attention did not have to be paid to the avoidance of blood cell destruction there was an obvious advantage in minimizing this and other untoward effects.

In 1905, Embley and Martin[20] devised an ingenious double circulation system that propelled the blood through the lung for oxygenation

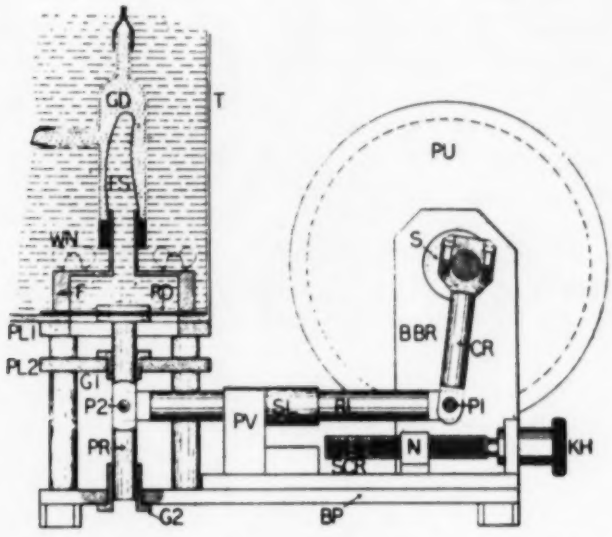

Fig. 4—The Dual Blood Pump of Dale and Schuster—1927. (From Dale, H. H. and Schuster, E. H. J.[21] in *Journal of Physiology* 64:356-84, 1927. Reprinted by permission of the publisher, Cambridge University Press.)

and then into the arterial tree for clearance through the kidney. They used a reciprocating type pump with rubber bladders compressed by the platforms. Variations of this system were employed thereafter until 1927 when Dale and Schuster[21] described their double perfusion pump in which an attempt was made to maintain sterility and avoid as much cell destruction as possible.

Mechanical improvements in the propulsion of blood have progressed with increasing knowledge of hemodynamics. The recent development of blood pumps is an attempt to meet the challenge of shunting blood outside the body for oxygenation or urea clearance with as little change in its physical characteristics as possible. The study of coagulation, changes in pH, osmotic pressure, viscosity, elasticity, turbulence and foaming is all part of this endeavor.

The Artificial Kidney

Ever since Ludwig's exposition of the nature of the function of the mammalian kidney, the idea of a mechanical substitute seemed a

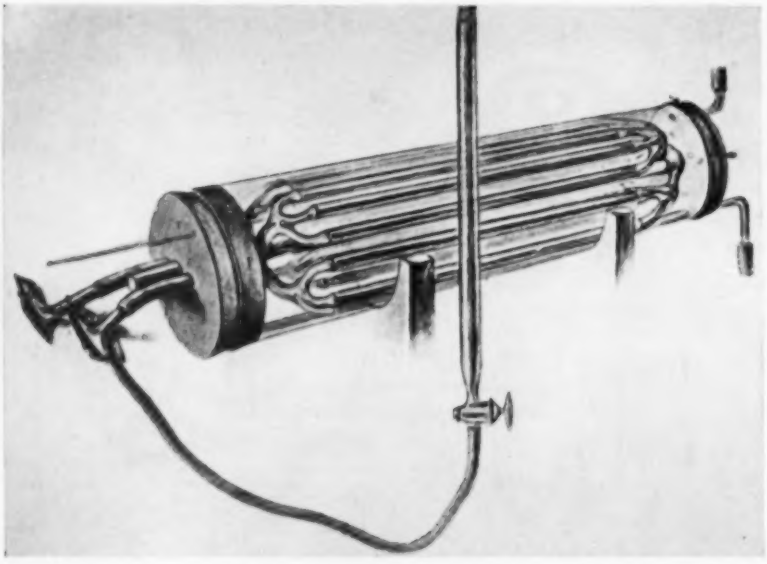

Fig. 5—Perspective View of Vividiffusion Apparatus; Earlier Form with Sixteen Tubes. The Artificial Kidney of Abel, Rowntree and Turner—1913. (From Abel, J. J., Rowntree, L. G. and Turner, E. B.[22] in *Journal of Pharmacology and Experimental Therapeutics* 5:276-316, 1913-14. Reprinted by permission of the publisher, Williams & Wilkins Co.)

feasible one. In 1913, Abel, Rowntree and Turner[22] described an apparatus which was capable of removing excessive amounts of salicylates from the circulating blood. They used an instrument through which an extracorporeal circulation was maintained with glass cannulas leading from an artery to a collodion tube spiral immersed in electrolyte solution and then back again to the animal. As anticoagulant, they used hirudin obtained from the ground heads of leeches. With this apparatus toxic levels of salicylate could be reduced by diffusion to within normal limits.

The concept was well presented. "In the hope of providing a substitute in such emergencies which might tide over a dangerous crisis, as well as for the important information which it might be expected to provide concerning the circumstances normally present in the blood, and also for the light that might thus be thrown on intermediary stages of metabolism, a method has been devised by which

the blood of a living animal may be submitted to dialysis outside the body and again return to the natural circulation without exposure to air, infection by microorganisms or any alteration which would necessarily be prejudicial to life."

A decade later the use of cross transfusion for the purpose of urea clearance was studied experimentally.[23] Because of the many technical problems this line of investigation was not followed for another twenty years.

In the midst of World War II, during the invasion of his homeland, Kolff[24] pursued the problem clinically. To him belongs the credit of making the artificial kidney a practical instrument. He used cellophane tubes with heparin as the anticoagulant.

The remarkable perfection of this apparatus by the team at the Peter Bent Brigham Hospital in this country is an outstanding accomplishment in recent years.[25]

Use of the Extracorporeal Shunt to Exclude the Heart

The idea of having the circulation of one animal supplying an organ of another under experimental conditions was a recognized procedure by the first decade of this century.[26] The application of this principle to take over the burden of the entire circulation of a companion animal is, however, an endeavor of the last decade. The necessity for rendering the heart bloodless in order to place its chambers within the realm of precise, unhurried surgery is obvious. For the use of a companion in this cross transfusion or parabiotic technique it is necessary to have a controlled, dual action pump which can exchange equal amounts of arterial and venous blood over some period of time without destroying the erythrocytes or defibrinating the plasma. The companion animal serves as the oxygenator in this technique.

This particular method has been the subject of intensive investigation by Blum and Megibow,[27] Lillehei and Warden,[28] Andreasen and Watson.[29] In the last year Lillehei has successfully applied this method for the definitive surgical cure of interventricular septal defects and the tetralogy of Fallot.

The other type of extracorporeal shunt to permit exclusion of the mammalian heart is dependent upon the employment of an oxygenator. In this method the blood is siphoned off from the venae cavae which have been clamped off and pumped into some type of apparatus which

films the blood while exposing it to pure oxygen. It is then collected and pumped back into the arterial tree. The early oxygenators depended upon the bubbling of oxygen through blood. This method was described as early as 1882.[30] Later investigators recognized the resultant foaming to be due to erythrocyte destruction which resulted in the ultimate death of the animal. It was soon evident that the answer to the problem lay in the filming of the moving blood over a large surface during its exposure to oxygen. Numerous ingenious devices have been employed. These include the silk mesh curtain of Richards and Drinker,[31] the revolving spiral sheet of Cruickshank,[32] the rotating glass cylinder of Frey and Gruber[33] and the multiple disks of Hooker.[34]

It was, however, Gibbon,[35] who after fifteen years of application devised his present apparatus which is remarkable for the efficiency of oxygenation and the avoidance of blood destruction. The intricate device that has been developed after years of ingenious travail has, however, not yet been consistently successful in its application to clinical problems. It appears that the chief defect is that of restoring the normal coagulating properties of the blood following the procedure. The propulsion of the blood stream in this particular apparatus is achieved by use of the peristaltic type of blood pump.

The applications of the extracorporeal shunting of blood are limitless. It is conceivable that this technique may ultimately lead to the replacement of viscera by prostheses designed to substitute for them. We are now merely on the threshold of exciting possibilities which the close collaboration of the physiologist, the physicist and the surgeon can transform into solid accomplishment.

REFERENCES

1. Exodus VII.
2. Zimmerman, L. M. Evolution of blood transfusion, *Bull. Soc. med. Hist. Chicago 5*, no. 4:44-54, 1943.
3. Success of the experiment of transfusing the blood of one animal into another, *Phil. Trans. roy. Soc. London 1*:352, 1666.
4. Letter concerning a new way of curing sundry diseases by transfusion of blood, written to M. deMontmer by J. Denis, *Phil. Trans. roy. Soc. London 1*:490, 1667.
5. Blundell, J. Observations on transfusion of blood, *Lancet 2*:321-24, 1828-1829.
6. Gesellius, F. *Capillar-Blut undefibrinirtes zur transfusion.* St. Petersburg, A. Muenz, 1868.
7. Landois, L. Auflösung der rothen Blutzellen, *Zbl. med. Wiss. 12*:419-22, 1874.
8. Landsteiner, K. Ueber Agglutinationserscheinungen normalen menschlichen Blutes, *Wien. klin. Wschr. 14*:1132-34, 1901.
9. Ottenberg, R. Studies in isoagglutionation; transfusion and the question of

intravascular agglutination, *J. exp. Med. 13*:425-38, 1911.

10. Lindeman, E. Simple syringe transfusion with special cannulas, *Amer. J. Dis. Child. 6*:28-32, 1913.
11. Unger, L. J. A new method of syringe transfusion, *J. Amer. med. Assoc. 64*: 582-84, 1915.
12. Poiseuille, J. L. M. Recherches sur la force du cœur aortique, *Paris Thesis*, 1828, p. 166.
13. Bordet, J. and Gengou, O. Recherches sur la coagulation du sang et les sérums anticoagulants, *Ann. Inst. Pasteur 15*:129-44, 1901.
14. Hustin, A. Principe d'une nouvelle méthode de transfusion muqueuse, *J. Med. Baux. 12*:436-39, 1914.
15. Agote, L. Hidrocefelia sifolitica, su tratamiento porel, neosalvarsan por via intracraneana, *An. Inst. mod. de clin. Med. Buenos Aires 1*:48-57, 1915.
16. Lewisohn, R. A new and greatly simplified method of blood transfusion, *Med. Rec. 87*:141, 1915.
17. Ewbank, T. *Hydraulic and other machines*. New York, Scribner, 1870.
18. von Issekutz, B. Beiträge zur Wirkung des Insulins, *Biochem. Z. 183*:283-97, 1927.
19. DeBakey, M. E. Simple continuous-flow blood transfusion instrument, *New Orleans med. surg. J. 87*:386-89, 1934.
20. Embley, E. H. and Martin, C. J. Action of anaesthetic quantities of chloroform upon the blood vessels of the bowel and kidney; with an account of an artificial circulation apparatus, *J. Physiol. 32*:147-58, 1905.
21. Dale, H. H. and Schuster, E. H. J. Double perfusion-pump, *J. Physiol. 64*: 356-84, 1927.
22. Abel, J. J., Rowntree, L. G. and Turner, B. B. On removal of diffusable substances from circulating blood by means of dialysis, *Trans. Assoc. Amer. Phycns. 28*:51-54, 1913; also in *J. Pharmacol. exp. Therap. 5*:275-316, 1913-1914.
23. Nyiri, W. Experimentelle Untersuchungen über gekreuzte Bluttransfusion bei Urämie, *Arch. exp. Path. Pharmak. 116*:117-24, 1926.
24. Kolff, W. J. Die kunstmatige nier. Kampen, Holland, J. H. Kok, 1946.
25. Merrill, J. P. The artificial kidney, *New Engl. J. Med. 246*:17-27, 1952.
26. Fredericq, L. Sur la circulation céphalique croissée ou échange de sang carotidien entre deux animaux, *Arch. Biol. 10*:127-30, 1890.
27. Blum, L. and Megibow, S. J. Exclusion of the dog heart by parabiosis, *J. Mt. Sinai Hosp. 17*:38-43, 1950.
28. Warden, H. E., Cohen, M., Read, R. C. and Lillehei, C. W. Controlled cross circulation for open intracardiac surgery, *J. Thorac. Surg. 28*:331-41, 1954.
29. Andreasen, A. T. and Watson, F. Report on experiments concerning a donor circulation, *Brit. J. Surg. 41*:195-206, 1953.
30. von Schroeder, W. Ueber die Bildungsstäte des Harnstoffs, *Arch. exp. Path. Pharmak. 15*:364-402, 1882.
31. Richards, A. N. and Drinker, C. K. An apparatus for the perfusion of isolated organs, *J. Pharmacol exp. Therap. 7*: 467-83, 1915.
32. Cruickshank, E. W. H. A magnetic blood oxygenator, *J. Physiol. 82*:26-32, 1934.
33. von Frey, M. and Gruber, M. Ein Respirationsapparat für isolirte Organe, *Arch. Anat. Physiol. 9*:519-22, 1885.
34. Hooker, D. R. The perfusion of the mammalian medulla; the effect of calcium and potassium on the respiratory and cardiac centers, *Amer. J. Physiol. 35*:200-08, 1915.
35. Gibbon, J. H., Jr. Present status of mechanical heart and lungs, *Med. Rec. Ann. 46*:872-76, 1952.

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Albert Lansing, Emory University School of Medicine, Atlanta, Ga.

PSYCHOLOGIC ASPECTS OF AGING
Ross A. McFarland, Harvard University

EXPERIMENTAL PROLONGATION OF THE LIFE SPAN
Clive M. McCay, Cornell University, Ithaca, N. Y.

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ARTHRITIS IN THE ELDERLY PATIENT
Joseph J. Bunim, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland

THE EFFECT OF AGING ON THE MYOCARDIUM
William Dock, State University of New York College of Medicine at New York City, Brooklyn, N. Y.

FLUID AND ELECTROLYTE PROBLEMS IN SURGERY OF THE AGED
Henry T. Randall, Memorial Center for Cancer and Allied Diseases

RELATION OF INCREASED LONGEVITY TO NEOPLASIA
C. P. Rhoads, Memorial Center for Cancer and Allied Diseases

Wednesday, October 12

SOME PHYSIOLOGICAL ASPECTS OF AGING — *Wesley M. Carpenter Lecture*
N. W. Shock, National Heart Institute, Bethesda, Maryland

NUTRITIONAL PROBLEMS OF ADVANCING AGE
Fredrick J. Stare, Harvard University

GASTROINTESTINAL HEMORRHAGE IN ELDERLY PATIENTS
Thomas P. Almy, Cornell University Medical College

Thursday, October 13

PANEL MEETING — CEREBROVASCULAR DISEASE WITH AGING
Chairman: Irving S. Wright, Cornell University Medical College

Friday, October 14

PANEL MEETING — PROBLEMS OF RETIREMENT
Chairman: Howard Reid Craig, Director, The New York Academy of Medicine

(Continued on next page)

Second Week

Monday, October 17

THE NATURE OF THE RESPONSE TO STRESS WITH AGING — *Harlow Brooks Lecture*
James L. Whittenberger, Harvard University

EVALUATION AND PREPARATION OF THE PATIENT WITH DEGENERATIVE CARDIOVASCULAR DISEASE FOR MAJOR SURGERY
John S. La Due, The New York Hospital

THE AGING LUNG
Dickinson W. Richards, College of Physicians and Surgeons, Columbia University

Tuesday, October 18

MANAGEMENT OF INJURIES IN THE AGED
Robert H. Kennedy, Beekman-Downtown Hospital, New York

MANAGEMENT OF SURGICAL EMERGENCIES IN THE AGED
Candict W. Cutler, Jr., Goldwater Memorial Hospital, New York

SURGERY OF CHRONIC DISEASES IN THE AGED
Frank Glenn, The New York Hospital

ANESTHESIA IN THE AGED
Emanuel M. Papper, Presbyterian Hospital

Wednesday, October 19

EMOTIONAL AND PSYCHIATRIC PROBLEMS OF AGING
Francis J. Braceland, The Institute of Living, Hartford, Conn.

NEUROSURGICAL TREATMENT OF PARKINSONISM
Irving S. Cooper, New York University-Bellevue Medical Center

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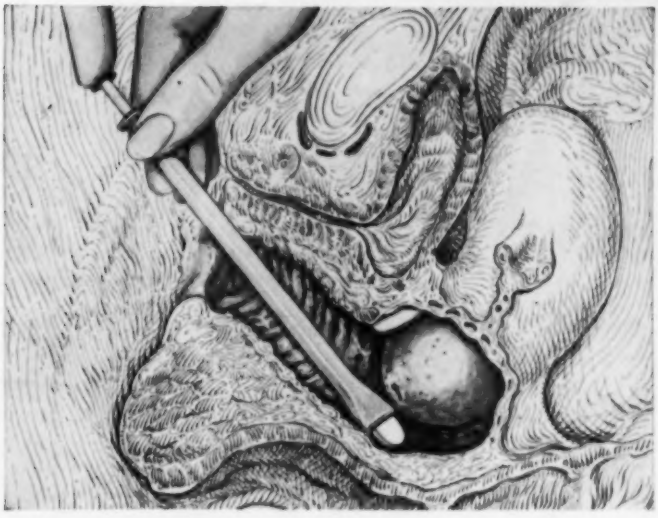

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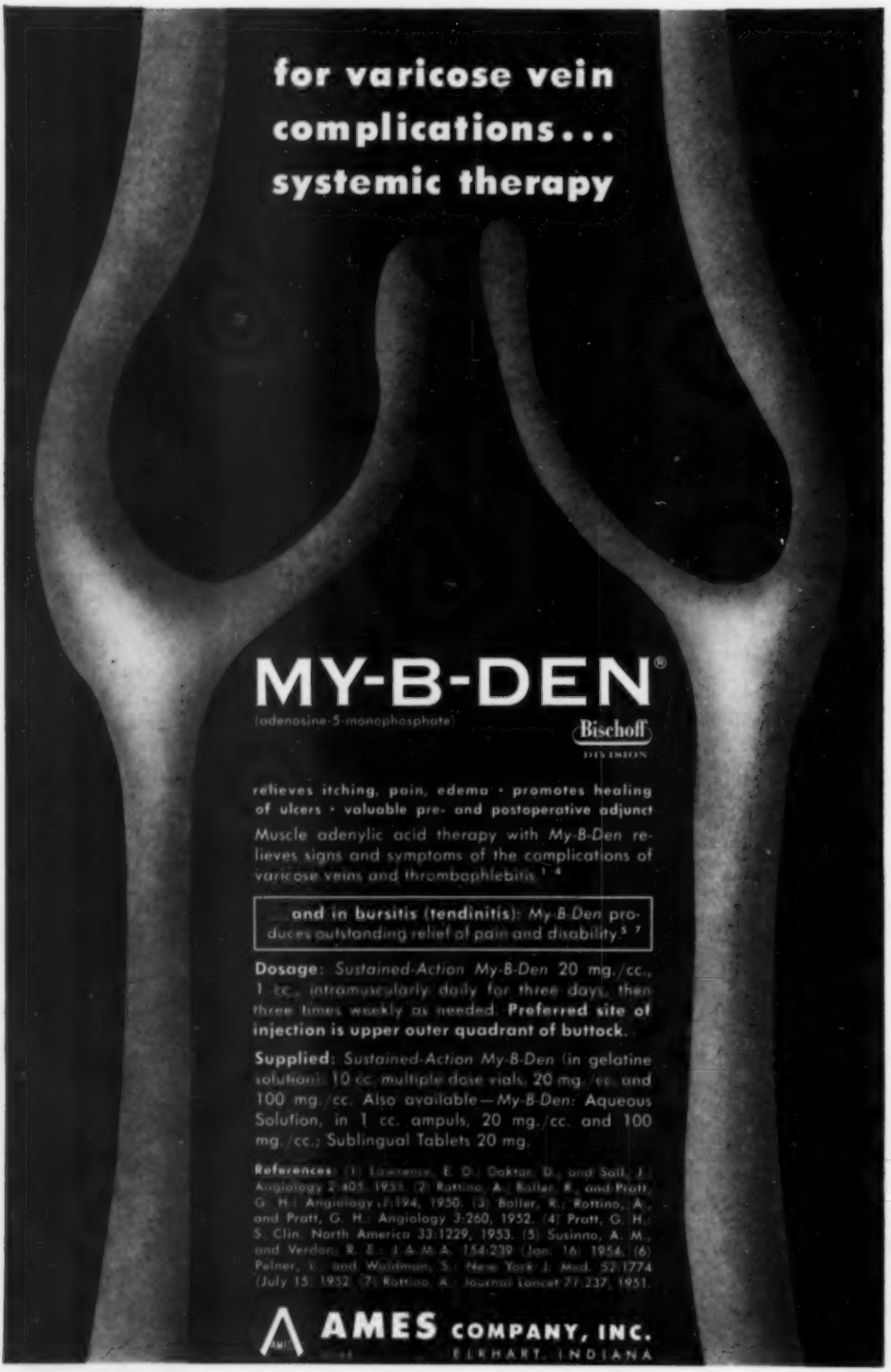
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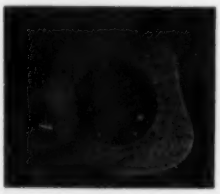

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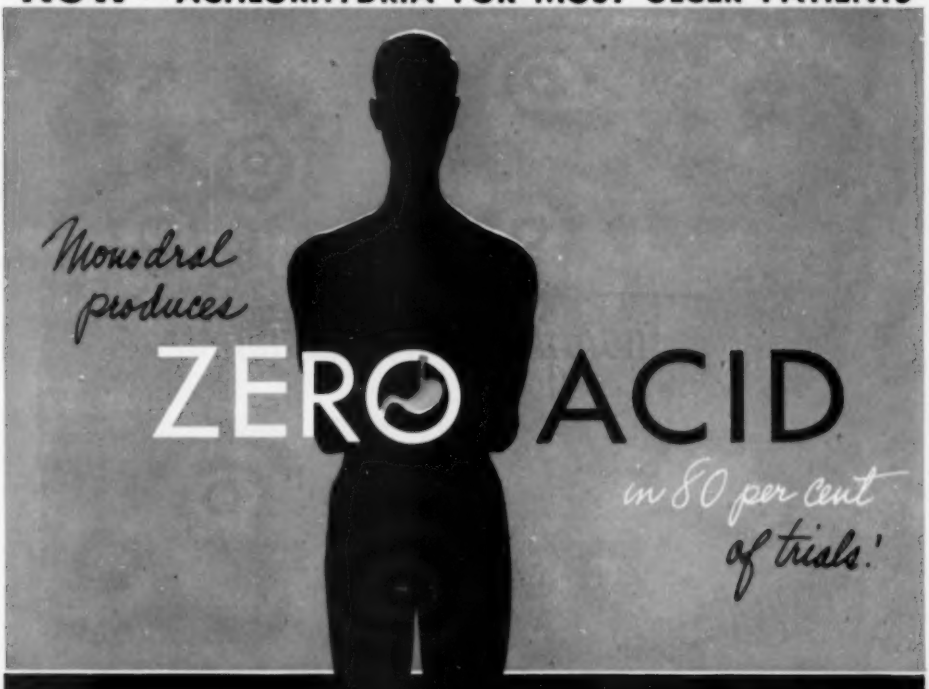

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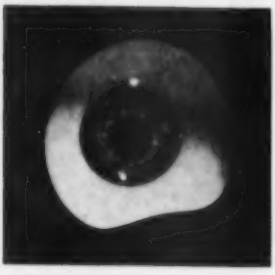

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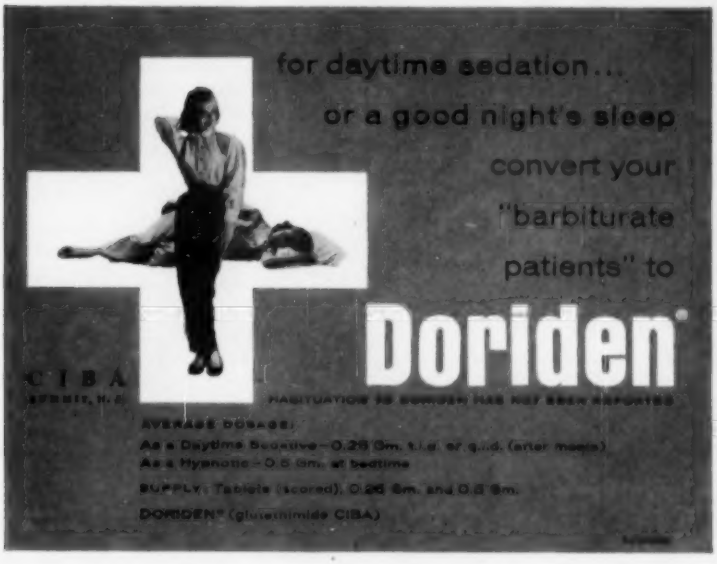

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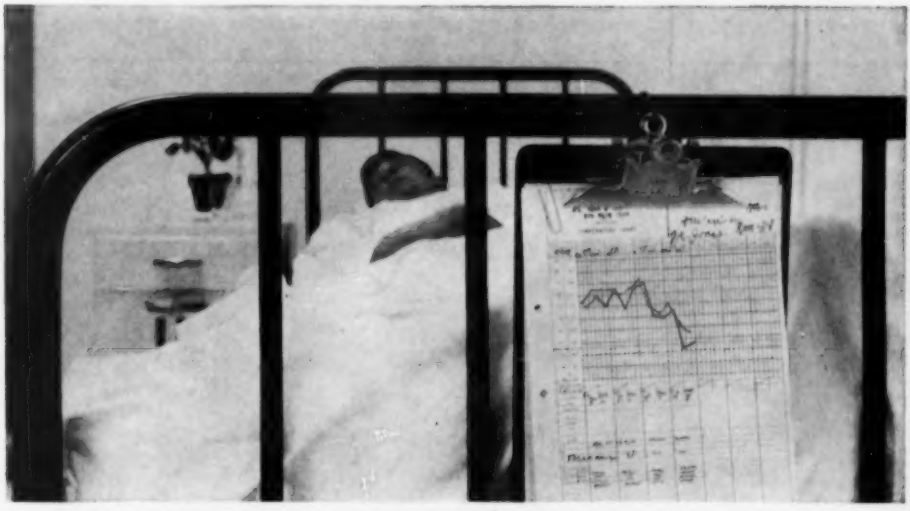

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1. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. *1*:296 (May) 1955. 2. Prigot, A.: Ann. New York Acad. Sc., in press. 3. Milberg, M. B., and Michael, M., Jr.: Ibid. 4. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952.

*Trademark for Pfizer brand of antibiotics with vitamins.
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1. Chamberlain, D. T.: Gastroent. 17:224-5, 1951. 2. McHardy, G., and Browne, D. C.: South. M. J. 45:1139, 1952. 3. Potula, S. F.: Postgrad. Med. 11:123, 1952.

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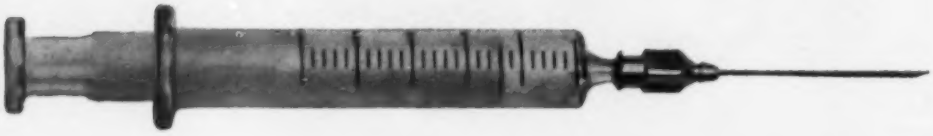

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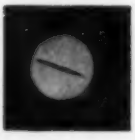

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